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MAY 1953

VOLUME 49 NUMBER 5

Published Monthly by
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Feb. 7, 1929, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $12.00

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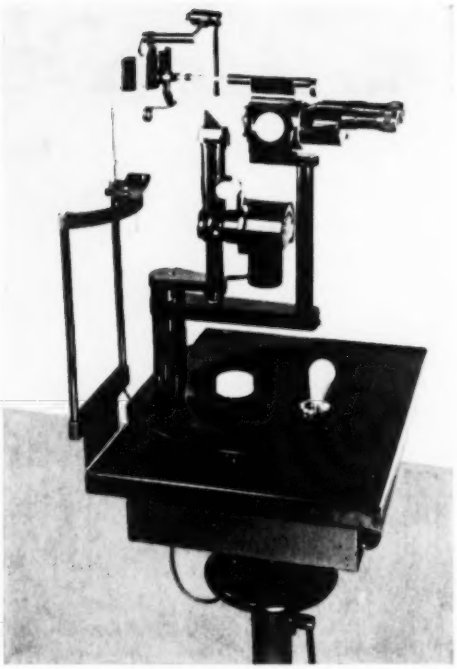

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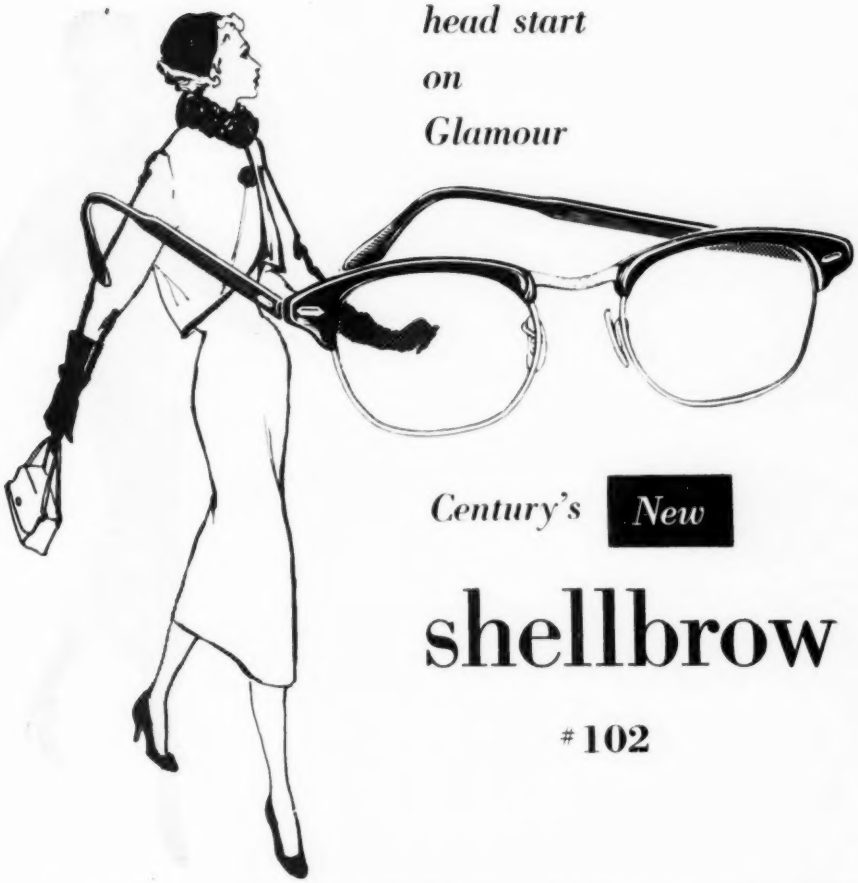

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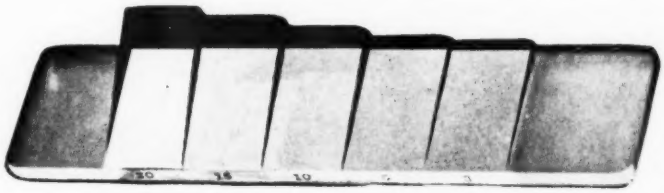

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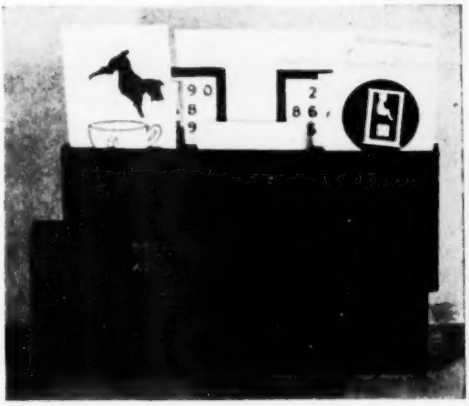

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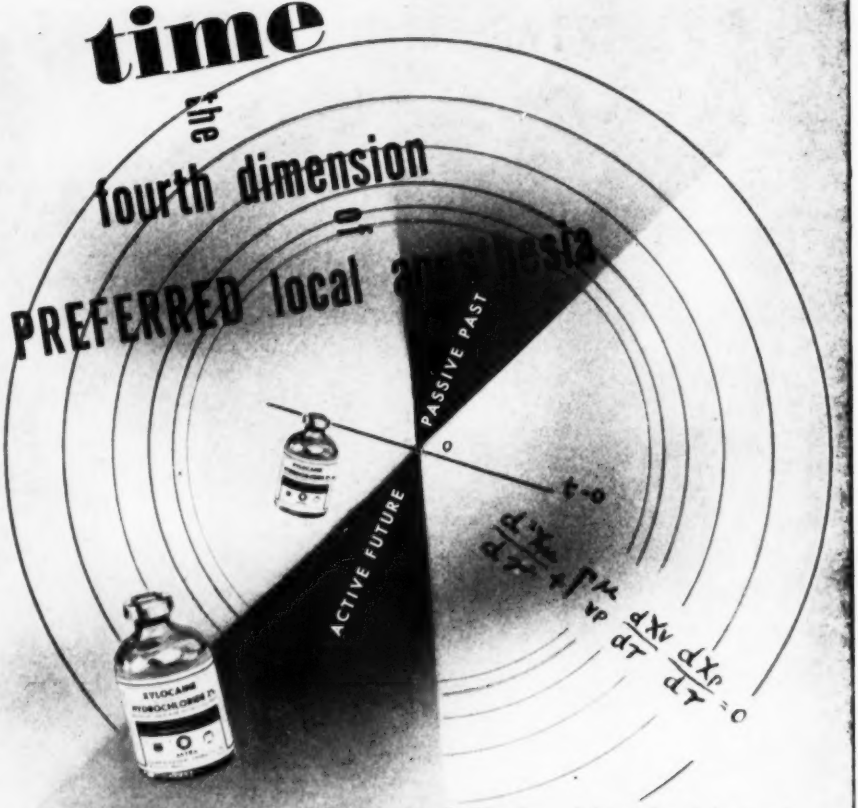

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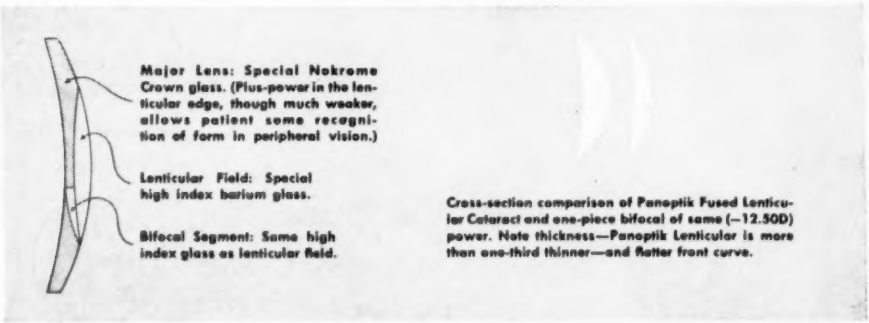
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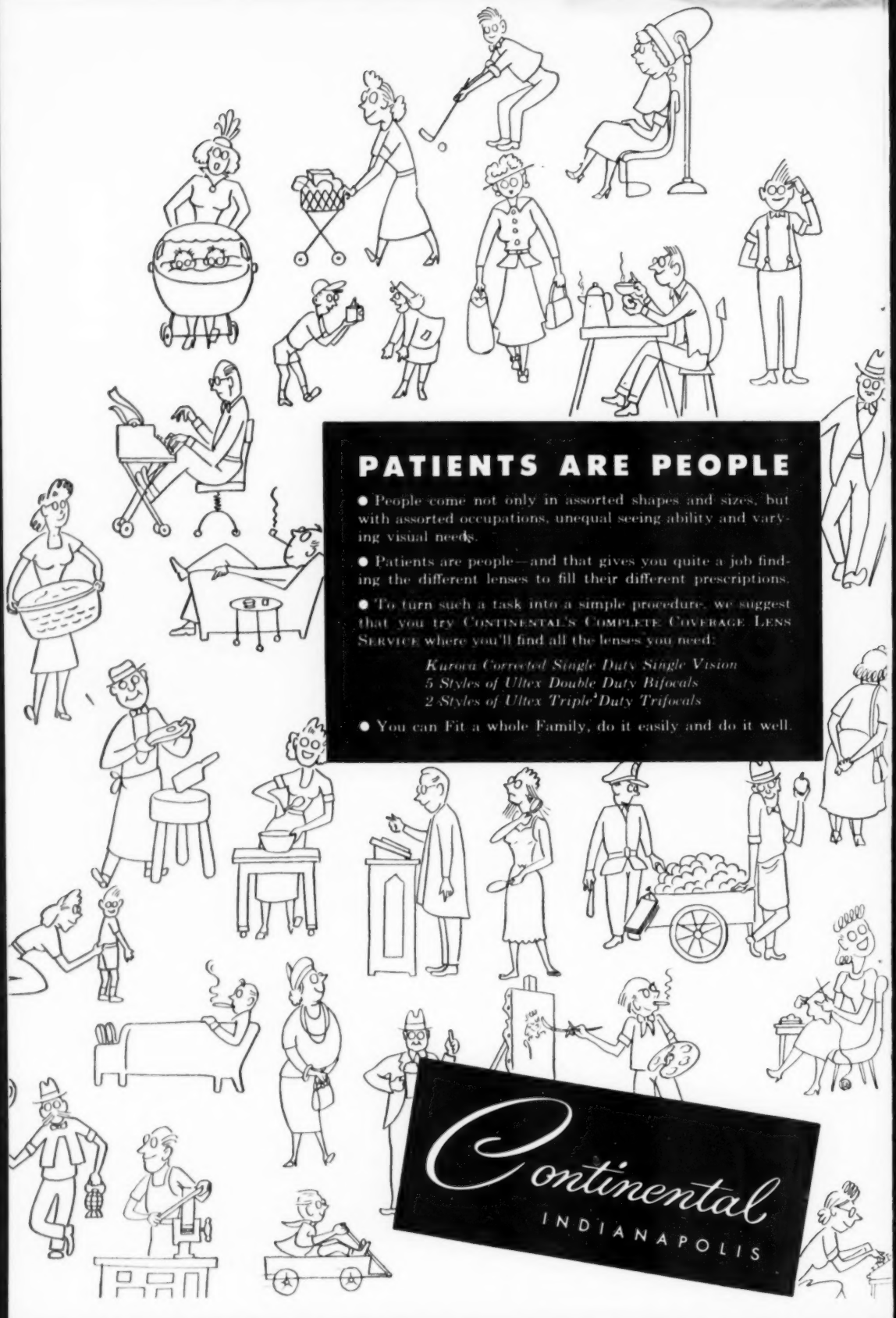
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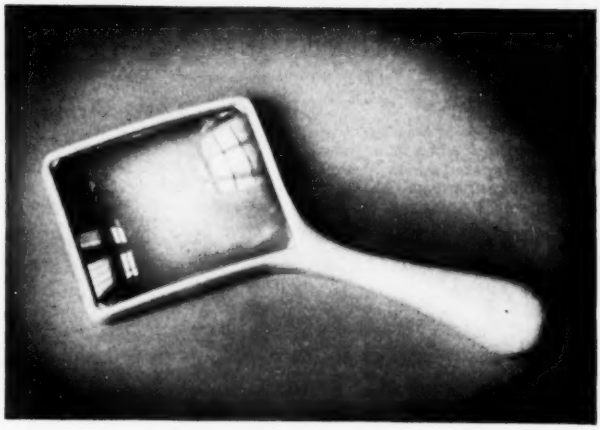

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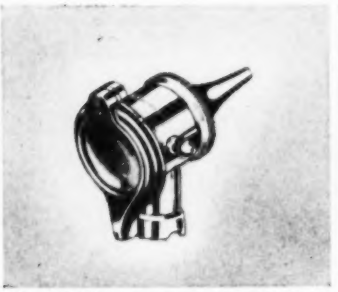

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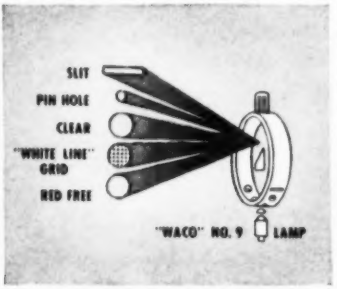

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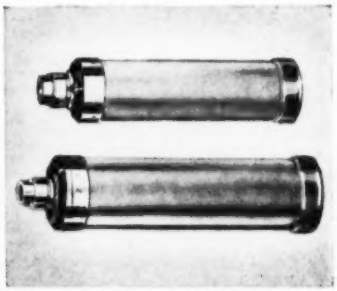

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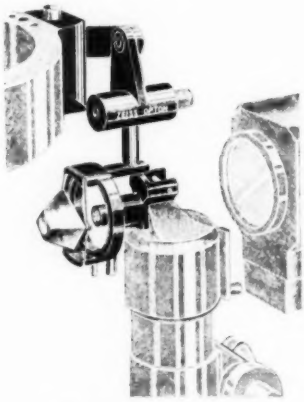

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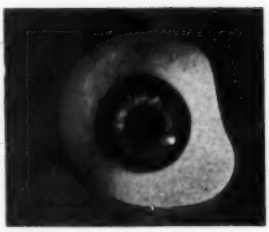

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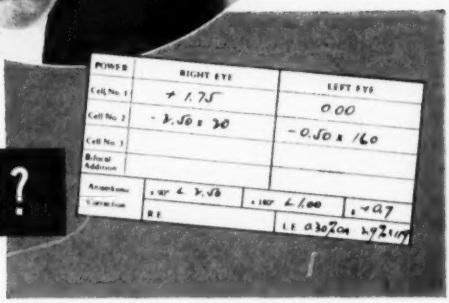

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ARCHIVES OF OPHTHALMOLOGY

VOLUME 49 MAY 1953 NUMBER 5

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PREANESTHETIC SEDATION AND ANALGESIA FOR INTRAOCULAR OPERATIONS DONE WITH LOCAL ANESTHESIA

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THE VALUE of individualized preanesthetic medication to produce effective sedation and analgesia for eye surgery is well recognized. This is particularly true of intraocular surgery done with local anesthesia. It is difficult to exaggerate the importance of good anesthesia and akinesia, and to obtain them careful attention to the details of the preanesthetic preparation of the patient is essential. Although the need for this is well known, many surgeons fail to give it the attention it deserves. Thus many operations are made more hazardous and eyes are needlessly damaged.

With the improved anesthesia and operative technique now generally practiced, it becomes increasingly difficult to decrease appreciably the number of mishaps in operations, such as those for cataract extraction. However, any measure that will improve our percentage of good results by even a fraction of 1% seems worthy of consideration.

Hartmann[1] has recently emphasized the importance of careful psychologic preparation of the patient for operation. He points out that the danger of complications is greater if the patient is disturbed and apprehensive. The truth of this statement cannot be overestimated. In preparing the patient for operation, each surgeon may have a different psychologic approach and yet reach the same goal. Certainly, a well-trained office and hospital personnel that inspires confidence is most helpful in reassuring the patient. An academic measure which is often given too little attention is the provision of a quiet, peaceful atmosphere for the patient prior to operation. We assume that this is the case; yet often we see the bed surrounded by chattering visitors, who stimulate rather than calm the patient. However, for the patient to know that a relative or close friend is near can have a comforting and soothing effect. Smaller doses of the sedative and analgesic may be sufficient and better anesthesia obtained for patients prepared under such circumstances.

In order to learn what preanesthetic sedation and analgesia is currently in favor, an inquiry was sent to a number of eye surgeons in the United States and in 16 other countries. The replies to these letters are most interesting and instructive. A brief analysis of the different methods used serves as a starting point from which to formulate a safe and effective preoperative procedure.

The 50 surgeons in the United States to whom I wrote all responded to my inquiry. They represent a good cross section of the eye surgeons in this country, and their responses merit careful study.

Read at the Fifty-Eighth Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., June 5, 1952.

1. Hartmann, E.: Préparation préopératoire de malade et du chirurgien en ophthalmologie, Ann. ocul. **184**:48-63 (Jan.) 1951.

Of these 50 surgeons, all but 2 use one of the barbiturates prior to operation to produce sedation for intraocular surgery done with local anesthesia. Of the two surgeons who do not use a barbiturate, one does not prescribe any sedative or analgesic and the other uses morphine and scopolamine.

Pentobarbital sodium (nembutal®) is the barbiturate used by 60% of the surgeons, and 30% use meperidine hydrochloride (demerol®) in addition to the pentobarbital sodium.

The next most popular barbiturate for preoperative administration is secobarbital (seconal®) sodium, which is used by 20% of surgeons, and the remaining 10% are about evenly divided among the use of amobarbital sodium (sodium amytal®), allonal® (allyl isopropyl barbituric acid and acetophenetidin), hexetol sodium (ortal® sodium), and chloral hydrate. It should be added that a number whose first choice is pentobarbital or secobarbital use chloral hydrate as an alternate when a barbiturate is contraindicated. The responses from Canada and South America showed the preanesthetic medication to be similar to that used in the United States.

In England, Scotland, and Australia, the preanesthetic medication is rather uniform. All who responded use a barbiturate, of which pentobarbital sodium and phenobarbital ("phenobarbitone") are equally popular. Amobarbital sodium is occasionally used as an alternate, and the combination of a mixture of the hydrochlorides of the opium alkaloids ("onmopon," pantapon®) and scopolamine is used in selected cases to supplement sedation.

On the European continent the barbiturates are used less frequently. Proprietary preparations such as "nargenol,"[2] "S. E. E." (scopolamine, eucodol, and "ephetonin")[3] or similar ones containing scopolamine, codeine or morphine, and ephedrine are the choice of a majority of the surgeons who answered my inquiry. Over 65% reported using a combination containing morphine and scopolamine. Three stated that they did not use any sedative or analgesic prior to anesthesia, and a fourth stated that he seldom used any.

Both here and abroad the time of administering the preanesthetic medication and the dose vary considerably. Over 60% of the surgeons in this country with whom I corresponded prescribe a test dose of the barbiturate the night before operation, and several also give an analgesic, such as meperidine, to disclose any idiosyncrasy to the drugs, as well as for the sedative effect. A few prescribe for nervous, apprehensive patients small doses of a barbiturate, to be taken for several days to a week prior to admission to the hospital for cataract extraction.

The time that the sedative is given on the day of operation ranges from 15 minutes to 3½ hours before the operation. Some surgeons who operate in the afternoon give a small dose of the sedative in the early morning and repeat as

2. "Nargenol" has the following composition:

Dihydroxycodeinone camphorsulfonate	0.02 gm.
Scopolamine camphorsulfonate	0.5 mg.
Ephedrine camphorsulfonate	0.02 gm.
Sparteine camphorsulfonate	0.05 gm.
Physiologic serum q. s.	2.00 gm.

3. "S. E. E." contains the following drugs in two strengths:

Scopolamine hydrochloride	0.5 mg.	1 mg.
Eucodal (dihydrohydroxycodeinone hydrochloride)	0.01 gm.	0.02 gm.
"Ephetonin" (synthetic racemic ephedrine hydrochloride)	25 mg. in each cc.	0.05 gm.

indicated to prevent the patient from becoming nervous and apprehensive. A larger dose is given 3½ hours before operation, and another dose is given 1 to 1½ hours before the operation, usually one-half the dose given at the 3½-hour period. The dose is regulated according to the amount of sedation desired and the effect already obtained.

As previously indicated, pentobarbital sodium is the most popular barbiturate for preoperative sedation. It is given orally, and the dose most commonly administered is 0.1 gm. 1½ hours before operation, although twice this dose (0.2 gm.) is used by some and given 3½ hours before operation, and another 0.1 gm. one hour before operation. One surgeon reported oral administration of pentobarbital sodium, 0.1 gm., 15 minutes before operation. There is apparently a great variation in the time of administration.

When more rapidly acting sedatives, such as secobarbital or chloral hydrate are used, the interval between the administration and the operation is often shortened to between 15 and 45 minutes.

In the United States meperidine hydrochloride and acetylsalicylic acid (aspirin) are the analgesics most commonly given concurrently with the barbiturates. A few advocate the use of scopolamine with meperidine. The favored time for administration of meperidine is 30 to 45 minutes before operation or "on call," which is estimated to be about 30 minutes before operation. Meperidine is also given in the operating room to supplement a dose given earlier.

A brief review of the well-known properties of the commonly used sedatives and analgesics may help in deciding the best method of producing preanesthetic sedation and analgesia for intraocular operations done with local anesthesia.

SEDATIVES

The barbiturates are excellent sedatives, particularly to produce preanesthetic sedation for intraocular operations, because they rarely cause nausea, vomiting, or other undesirable effects when used carefully. However, if the pharmacology and toxicology of these drugs are not kept in mind, unhappy side-reactions may occur.

All the barbiturates have the same general type of depressant action on the central nervous system. The major differences are in the rapidity of action and the duration of the depressant effect. Any degree of depression, from slight sedation to deep coma, can be obtained with the barbiturates, but in a sedative dose they are said not to produce analgesia, and may cause delirium in the presence of pain. Sedation and sleep occur in 15 to 60 minutes and last five to seven hours. Recovery from an overdose of barbiturate may be accompanied by restlessness, during which the patient may be irrational and hyperactive,[4] a point of some importance after intraocular surgery. Disorientation occurs more frequently in elderly patients after the administration of barbiturates, particularly the longer-acting ones. Patients with an idiosyncrasy to the barbiturates may become excited and as unmanageable as a patient with acute alcoholism.

The barbiturates are said to counteract the toxic action of local anesthetic agents. However, according to Seevers,[5] the quantity of the barbiturate ordinarily admin-

4. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941.

5. Seevers, M. H.: The Preparation of the Patient, Tr. Am. Acad. Ophth. **53**:281-287 (March-April) 1949.

istered is entirely inadequate to prevent anything but the most minor manifestations of toxicity from the local anesthetic agent. Other excellent authorities [6] state that the barbiturates decrease the toxic results of local anesthetics and not only arrest convulsions due to an overdose of the local anesthetic but also increase the minimal lethal dose of the local anesthetic three to four times. This does not apply to the rare occasion on which a small amount of the local anesthetic causes sudden cardiovascular collapse, which should be classified as an idiosyncrasy.

The barbiturates tend to decrease the general tonus of the intestinal musculature,[7] an action which may account for the beneficial effect when they are prescribed for nausea and vomiting of functional origin.

There are fewer contraindications to the use of barbiturates than to most of the sedatives, but these should be kept in mind. Untoward reactions are more likely to occur in patients with fever, hyperthyroidism, diabetes mellitus, and severe anemia. In Parkinson's disease the muscular rigidity may be aggravated to the extent that the patient becomes bedridden.[4]

The dose should be carefully calculated after a critical study of the patient. It is sometimes forgotten that smaller doses should be prescribed for elderly, debilitated patients and for Negroes and orientals, while larger doses are required for the younger, robust patients, those with hyperthyroidism, and highly excitable patients.

There seems no logical reason for trying to time the administration of the barbiturate so that the beginning of the maximum effect of the sedative exactly coincides with the administration of the anesthetic, since the maximum effect of the barbiturate persists several times the length of the average operation on the eye. It can be administered in ample time before the operation so that if there is not sufficient sedation more can be given and the maximum sedation be thus obtained before the patient leaves his room. In this way the fear experienced by many patients when being taken to the operating room is avoided.

CHLORAL HYDRATE

A large majority of those who answered my inquiry administer chloral hydrate if barbiturates are contraindicated. A few surgeons mentioned it as their first choice. According to Goodman and Gilman,[4] chloral hydrate is one of the oldest and best hypnotics but has little analgesic power. They consider it too hygroscopic to be prescribed in capsules, in which form it cannot be given without causing gastric irritation, and they recommend giving it well diluted in water or milk, with syrup or orange or citric acid to mask the taste, or rectally. With the sedative dose for the average adult of 0.5 to 2.0 gm., sedation is produced in 10 to 15 minutes, and sleep occurs within the hour and lasts five to eight hours. There are usually no unpleasant after-effects. Chloral hydrate rarely causes excitement or delirium except in the presence of pain, which it dulls somewhat when large doses are given.

It is an excellent alternate for the barbiturates, particularly in the case of elderly patients, and with other patients might be given preference over the barbiturates.

6. Tatum, A. L.; Atkinson, A. J., and Collins, K. H.: Acute Cocain Poisoning: Preliminary Report of an Experimental Study, J. A. M. A. **84**:1177 (April 18) 1925.

7. Quigley, J. P., and Phelps, K. R.: Observations Regarding Mechanism of Gastro-Intestinal Inhibition by Barbituric Acid Compounds, J. Pharmacol. & Exper. Therap. **50**:420-424 (April) 1934.

MORPHINE

Of the analgesics morphine is probably our most powerful, but the majority of ophthalmologists are of the opinion that it is contraindicated for intraocular surgery because it frequently causes nausea and vomiting. The intravenous use of morphine, scopolamine, and ephedrine, reported by Jensen, Haffly, and Sarro [8] is impressive. However, the comparatively small margin of safety with such potent drugs as morphine and scopolamine, particularly in elderly patients, should be thoughtfully considered. A few surgeons who answered my query claimed that morphine when given intravenously is less likely to produce nausea and vomiting. The rapid narcotic effect which occurs when it is administered intravenously is said to forestall the emetic effect of the morphine, although Gilman [9] states that he knows "of no pharmacological reason that morphine given intravenously should produce fewer side-effects than when given by intramuscular injection." The addition of scopolamine to counteract nausea incident to the use of morphine is advocated by a few surgeons. Scopolamine causes delirium with sufficient frequency to make it undesirable for intraocular operations. Morphine may also cause constipation, flatulence, and abdominal distention. Since effective analgesia can be obtained with meperidine, which does not cause as many undesirable side-reactions as morphine, there seems no good reason to use morphine as a preanesthetic medication for intraocular surgery.

MEPERIDINE HYDROCHLORIDE

A rapidly increasing number of eye surgeons are using meperidine hydrochloride (isonipecaine) in addition to a barbiturate for preanesthetic medication. Although used as a substitute for morphine, this compound is unrelated to morphine in structure.

In therapeutic doses meperidine has potent analgesic properties, a slight sedative action, and an antispasmodic effect. For preanesthetic medication it is administered chiefly for its analgesic property; incidentally, it greatly decreases corneal sensitivity. That only a slight sedative effect is obtained with this drug is not an objection because ample sedation can be produced by a barbiturate, which is usually given concurrently with the meperidine.

The spasmolytic action of meperidine, which obviates constipation, makes its use more desirable than that of morphine, codeine, or other opiate for the relief of pain. The antispasmodic action on the bronchi makes breathing easier for asthmatics with labored breathing, a point of some importance at the time of operation.

Besides these main actions, meperidine produces euphoria, and in conjunction with the barbiturates it induces amnesia. When the barbiturates are used with meperidine, they are effective in smaller doses than when used alone.

Meperidine produces very little respiratory depression and a minimal amount of nausea and vomiting as compared with morphine. It is said [10] to increase resistance to the effect of epinephrine on the heart, an action which is desirable.

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8. Jensen, C. D. F.; Haffly, G. N., and Sarro, L. J.: Use of Intravenous Morphine in Ocular Surgery, Am. J. Ophth. **33**:98-106 (Jan.) 1950.

9. Gilman, A.: Personal communication to the author.

10. Nickerson, M., and Smith, S. M.: Protection Against Cyclopropane-Epinephrine Arrhythmias by Dibenamine and Other Agents, Anesthesiology **10**:562-576 (Sept.) 1949.

The dose of meperidine hydrochloride for the average adult of 70 kg. (about 150 lb.) is 50 to 150 mg. The drug is usually given by intramuscular injection, although it may be administered orally or intravenously. It is not given subcutaneously, owing to the irritation it causes.

When meperidine is given intramuscularly, the analgesic effect is apparent in 15 minutes, but the maximum effect is not reached for 45 to 60 minutes or more and lasts two to six hours. Rovenstine and Batterman [11] found that 45 to 90 minutes is the optimal time that should elapse after the administration of meperidine before induction of the anesthesia is begun. After intravenous injections the effect becomes apparent almost immediately, and the full effect is reached in about 15 minutes. When meperidine is taken by mouth, its analgesic effect is apparent within 20 to 60 minutes. To obtain the maximal effect requires a longer time.

A number of surgeons who answered my inquiry expressed the opinion that meperidine when given intravenously is less likely to cause nausea and vomiting. However, a communication [12] from the pharmaceutical firm which produces meperidine states that "gastrointestinal disorders and dizziness are encountered infrequently, and then usually in cases in which the intravenous route of administration has been used," and their directions for administration advise that "intravenous administration does not offer sufficient advantages over the intramuscular injection to warrant this method."

If, for special reasons, the intravenous use of meperidine is indicated, the following precautions should be observed: The drug should be diluted with 3 to 5 cc. of isotonic sodium chloride solution or distilled water and injected slowly, two to three minutes being allowed for the injection. Use of a 27-gauge needle curbs the tendency to inject the solution rapidly. Rapid injection increases the severity and frequency of side-effects.

Meperidine is usually well tolerated and rarely produces toxic reactions when given in therapeutic doses. As with many drugs, however, patients may occasionally be sensitive to meperidine. This makes it advisable to administer a test dose before the day of operation, particularly when intraocular surgery is to be done. Intracranial lesions are said [13] to be a contraindication to the use of meperidine because of the depressant effect on respirations in such cases.

The replies to my inquiry suggest a few points in regard to the timing of the administration of meperidine that should be considered. The most active property of meperidine is analgesia, which, it is assumed, is the property for which it is usually selected by most surgeons for preanesthetic medication. The full effect of the analgesia is needed most when injections for local anesthesia are being given. After the administration of the local anesthetic, the analgesia produced by the meperidine should no longer be required. However, if the anesthesia is not complete, the analgesia may help to prevent pain caused by the operation.

If meperidine is given less than 45 to 60 minutes before operation, the maximum effect may not be reached by the time administration of the anesthetic is begun. If

11. Rovenstine, E. A., and Batterman, R. C.: Utility of Demerol as Substitute for Opiates in Preanesthetic Medication, Anesthesiology **4**:126-134 (March) 1943.

12. Wiener, H.: Personal communication to the author.

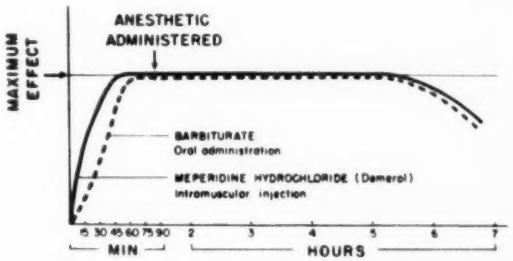
13. Guttman, S. A.: Demerol: Caution in Administration to Patients with Intracranial Lesions, J. A. M. A. **124**:155-157 (Jan. 15) 1944.

the dose is correct and administration of the barbiturate and analgesic has been well timed, there should be ample sedation and analgesia at the time the anesthetic is administered. The smallest dose of each that will produce the desired effect should be the aim if undesirable reactions are to be minimized.

Comparatively little analgesia is required if the local anesthetic is administered slowly and carefully, so that often a less potent analgesic than meperidine may be used. For years acetylsalicylic acid has been used for its analgesic property, along with a sedative. Since acetylsalicylic acid is known to cause gastric irritation, this drug is being replaced as an analgesic by "bufferin," a preparation of acetylsalicylic acid with aluminum aminoacetate and magnesium carbonate, which is said to buffer the acetylsalicylic acid so that it is less likely to produce gastric irritation.

CODEINE

Many surgeons reported using codeine in combination with other drugs for preanesthetic medication and for the relief of postoperative pain, although this drug is a relatively weak analgesic with minimal sedative effect as compared with meperi-



Curve showing sedative and analgesic given 90 minutes before the anesthetic is to be administered, so that the maximum effect will be obtained before the patient is taken to the operating room, an experience which many fear.

The maximum effect is shown to last several hours, a period which is ample for any operation on the eye.

dine. Codeine also has the undesirable property, similar to that of other opium derivatives, of causing constipation. Probably its greatest value is for the relief of cough.

NAUSEA AND VOMITING

The question of how often nausea and vomiting occur after operations on the eye done with local anesthesia was included in my inquiry. The answers indicated that its occurrence varied from a negligible number to 40% of the cases. One surgeon who estimated that this complication occurred in 30% of his cases and in approximately the same percentage in the other eye services in the same hospital made an interesting and practical comment. If the eye is doing well, the surgeon frequently may not read the nurses' daily notes or inquire concerning the occurrence of nausea, and so may have the impression that his patients have none. It is his opinion that nausea after local anesthesia is commoner than most surgeons realize.

One surgeon reported that the addition of scopolamine to the meperidine reduced nausea and vomiting to a minimum. Since meperidine has a parasympathetic effect similar to that of scopolamine, the addition of scopolamine hardly seems indicated, particularly as it is more likely to cause delirium. Another surgeon reported the use of phenobarbital (luminal®) sodium, 130 mg. intramuscularly, to control the nausea and vomiting, or of 5% dextrose in saline solution intravenously. Two reported using dimenhydrinate (dramamine®) before and after operation to control it. One used a suppository of dimenhydrinate, 100 mg., routinely after operation. Many expressed the opinion that the nausea and vomiting are functional and due to apprehension and fear. Others felt that nausea and vomiting are due to pain in the eye rather than to the medication used. Most of the surgeons who answered this question stated that nausea and vomiting are rare except after operations for detachment of the retina and on the extraocular muscles. After such operations nausea was found to occur frequently, and a few stated that it occurred after all such operations.

When I first used meperidine, three of the first five patients for cataract extraction to whom it was given vomited after the operation. Its use was discontinued for a time. Subsequently, it was again employed, its administration being preceded by 50 mg. of dimenhydrinate, given at 7:30 and 11:30 a. m. for patients to be operated on in the afternoon. Nausea then rarely occurred.

"Avomine,"[14] a derivative of promethazine hydrochloride, is also an antihistaminic agent used to treat motion sickness. I have found it to be more effective than dimenhydrinate. Both these drugs add to the sedation, and no undesirable side-reactions have been observed. Since "avomine" is not on the market in this country, I now use as a substitute a similar preparation, "phenergan" hydrochloride,[15] which so far seems equally effective, although I have not used it in a sufficient number of cases to form a definite opinion as to its efficiency. In a small series, including 24 diathermy operations for glaucoma, a procedure after which pain and nausea are likely to occur, only one patient was nauseated.

COMMENT

In the psychologic preparation, a nurse or another patient who has had a similar operation can often put the patient at ease more readily than the surgeon.

Whether pentobarbital sodium or secobarbital sodium is used as a sedative apparently makes little difference. Both are excellent sedatives, although pentobarbital is the drug more frequently chosen not only by eye surgeons but by others. It has been reported,[16] although contrary to the general belief, that pentobarbital sodium is more satisfactory than morphine for preanesthetic medication, even prior to general surgery. A series of cases has been reported[17] in which pentobarbital sodium given intravenously in hypnotic doses relieved pain in 50% of patients, as

14. Avomine is promethazine-8-chlorotheophyllinate, marketed by May & Baker, Ltd., Dagenham, England.

15. "Phenergan" hydrochloride is 10-(2-dimethylaminoisopropyl)-phenothiazine hydrochloride, marketed by Wyeth Inc., Philadelphia.

16. Cohen, E. N., and Beecher, H. K.: Narcotics in Preanesthetic Medication: A Controlled Study, J. A. M. A. **147**:1664-1668 (Dec. 22) 1951.

17. Keats, A. S., and Beecher, H. K.: Pain Relief with Hypnotic Doses of Barbiturates and Hypothesis, J. Pharmacol. & Exper. Therap. **100**:1-13 (Sept.) 1950.

compared with 80% relieved with morphine. These, and other, reports have influenced the selection of pentobarbital sodium as the sedative for intraocular operations.

Meperidine hydrochloride given in conjunction with a barbiturate is considered to be the most effective analgesic. If this drug is contraindicated, though this is rare, buffered acetylsalicylic acid may be used. Sedation is a minor property of meperidine, but since the drug has been shown to be safe in large doses and rarely produces serious side-effects, except nausea, it might be used without the barbiturates. Indeed, the use of meperidine in larger doses with an antihistaminic drug, such as "avomine," dimenhydrinate, or "phenergan," to prevent nausea might simplify the preanesthetic medication and deserves investigation.

A safe stage of sedation for intraocular operations is one in which the patient is amnesic, but still mentally cooperative, and in which the mental sedation is sufficient to produce a feeling of euphoria and a lack of concern about the operation. By cooperation is not meant that the patient is expected to assist by looking down and not squeezing the lids, as was expected of him years ago. These precautions are all taken care of by anesthesia, akinesia, and placement of sutures under the rectus muscles. With too much sedation the patient may not be able to cooperate, even to the extent of lying quietly on the table. He may snore peacefully throughout most of the operation and at a critical moment jerk his head or put up his hand. With oversedation there is also the danger that after the patient returns to his bed he may be irrational and damage his eye if he is not watched constantly.

The preparation of the patient and the drugs used to produce sedation and analgesia are frequently left to the resident. Often he has just finished a medical or surgical internship and has definite ideas in regard to sedation and analgesia, and time has not dulled his knowledge of pharmacology and therapeutics. The ophthalmologist who has not given this subject much thought for some years is amenable to suggestions and is usually glad to delegate this important matter to the resident. While the resident has at his finger tips the pharmacology and therapeutics of the various sedatives and anagesics and their use for general medical and surgical cases, he may not be as familiar with the contingencies in eye surgery that contraindicate and govern their use. Undoubtedly excellent sedation and analgesia can be produced with many different drugs and combinations. Our problem is to select the ones best suited for each particular patient and operation. Careful attention by the surgeon to the details of preanesthetic preparation is well worth the time involved.

SUMMARY

1. Careful psychologic preparation of the patient is important.

2. Mild sedation for at least 24 hours preceding the operation to relieve apprehension and produce a calm, tranquil patient is desirable.

3. Administration of test doses of all the drugs to be used prior to intraocular operations is advisable at least a day before the operation.

4. Timing the administration of the drugs is of paramount importance in order that the maximum effect of the sedative and analgesic may be reached at the time the anesthetic is administered.

5. For the average adult of 70 kg. (150 lb.) the following test dose is given at least one day before operation, usually the night before:

Pentobarbital sodium (nembutal*)	100 mg.
Meperidine hydrochloride (demerol*)	25 mg.
Promethazine-8-chlorotheophyllinate ("avomine") (or another antihistaminic drug, such as "phenergan" hydrochloride, 12.5 mg., to decrease the incidence of nausea)	25 mg.

If there are no untoward effects from the test dose, "avomine" or "phenergan" hydrochloride may be given two hours before operation and the following medication 1½ hours before operation:

Pentobarbital sodium	100-200 mg.
Meperidine hydrochloride	50-100 mg.

At the end of one hour, if there is insufficient sedation, another dose of pentobarbital sodium is advocated, the amount depending upon the patient and degree of sedation already obtained.

6. The smallest dose of both the sedative and the analgesic that will produce the desired effect should be the aim if undesirable reactions are to be minimized.

CONCLUSION

With careful preanesthetic preparation and medication, intraocular operations are made safer and easier.

EFFECTS OF EXPERIMENTALLY DECREASED OR INCREASED OXYGEN SUPPLY IN SOME OPHTHALMIC DISEASES

Practical Value for Diagnosis, Prognosis, and Treatment

GIAMBATTISTA BIETTI, M.D.
PARMA, ITALY

ANOXIA

THE EFFECTS of anoxia on the normal visual apparatus are well known,[1] and my collaborators and I have made a number of contributions to this field.[2] I should like only to recall that anoxia is able to produce changes in the neurosensory activity, in the intraocular circulation, in the intrinsic and extrinsic ocular

Professor of Ophthalmology and head of the Department of Ophthalmology, University of Parma.

Read before the Section of Ophthalmology at the One Hundred First Annual Session of the American Medical Association, Chicago, June 11, 1952.

1. (*a*) McFarland, R. A.; Evans, J. N., and Halperin, M. H.: Ophthalmic Aspects of Acute Oxygen Deficiency, Arch. Ophth. **26**:886, 1941. (*b*) Mercier, A., and Duguet, J.: Physio-Pathologie oculaire de l'aviateur, Bull. Soc. opht. Paris, pp. 440, Nov.-Dec., 1947. (*c*) Giardini, A.: Il comportamento dell'apparato oculare alle alte quote, Boll. ocul. **28**:649, 1949; Riv. med. aeronaut. **12**:565, 1949.

2. (*a*) Bietti, G. B.: L'occhio ed il volo (Note informative per l'aviatore), Riv. med. aeronaut. **9**:43, 1946. (*b*) Bietti, G. B., and Scano, A.: Influenza dell'anossia sui movimenti oculari: I. Azione sui movimenti dell'occhio nella lettura, ibid. **9**:12, 1946; (*c*) Contributo allo studio della circolazione retinica nella visione nera degli aviatori, ibid. **9**:138, 1946; (*d*) Ricerche di pupillografia in anossia, ibid. **11**:117, 1948. (*e*) Bietti, G. B., and Lo Monaco-Croce, T.: Variazioni della pressione arteriosa retinica e omerale, del tono endo-oculare e del quadro endo-otto-scopico nella anossia, ibid. **4**:177, 1941. (*f*) Bietti, G. B., and Giardini, A.: Influenza dell'anossia sui movimenti oculari: II. Ricerche comparative sull'azione dell'anossia e dell'alcool da soli o associati, ibid. **12**:198, 1949; (*g*) Influenza dell'anossia sui movimenti oculari: III. Azione dell'anossia sul potere di fusione delle immagini retiniche, ibid. **12**:339, 1949. (*h*) Bietti, G. B., and Ferraris de Gaspare, P. F.: Gli effetti dell'inalazione di ossigeno su zone scotomatose del campo visivo, Boll. ocul. **29**:29, 1950. (*i*) Bietti, G. B.: L'action de l'oxygène sur les fonctions rétiniennes: Son emploi en clinique, Bull. et mém. Soc. Franc. opht. **63**:195, 1950; (*j*) L'azione dell'ossigeno su alcune funzioni oculari: Possibilità di una utilizzazione pratica, Riv. med. aeronaut. **14**:42, 1951. (*k*) Boles Carenini, B., and Brognoli, C.: Sulla possibilità di influenzare con mezzi medicamentosi le alterazioni della macchia cieca e degli angioscotomi da anossia, ibid. **15**:274, 1952. (*l*) Boles Carenini B., and Cima, V.: Studi cul comportamento del senso cromatico (equazione de Rayleigh) all' anomaloscopio di Nagel sotto alterato apporto di Ossigeno all'apparato oculare, ibid. **15**:527, 1952. (*m*) Ferraris de Gaspare, P. F. and Boles Carenini, B.: Dell'azione del tabacco e dell'alcool sulla sensibilità retinica rilevata con lo scotoma artificiale di Goldman: Effetti della loro associazione con l'anossia, ibid. **15**:388, 1952; (*n*) Del meccanismo d'azione dello ossigeno sulla funzionalità retinica, ibid. **14**:3, 1951. (*o*) Ferraris de Gaspare, P. F., G.: Variazioni audiometriche del soggetto glau-

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motility, and in the normal transparency of the ocular media. As a general rule, one may assume that anoxia has a twofold influence on the visual organ: a direct one, and an indirect one, through general, nervous, and circulatory mechanisms.

Neurosensory Activity.—It is known, first of all, that there is in anoxia a reduction of the central visual acuity,[3] which is especially pronounced at low illumination.[4] I noted a comparable reduction in the resolving power of the retina.[2x] The visual field shows a slight concentric narrowing,[5] whereas the blind spot, as well as the angioscotomata, shows some enlargement.[6] All these changes are, indeed, not very pronounced, and the angioscotomata may even be reduced in size (in 20% of the cases according to my experience). Impairment of the light sense is, on the contrary, pronounced even at low altitudes.[7] The type and frequency of changes in the color sense are still the objection of discussion.[8]

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comatoso in anossia, Minerva otorinolaring. **14**:178, 1951. (*p*) Giardini, A.: Ricerche sui rapporti intercorrenti fra senso luminoso, anossia e glicemia, Riv. med. aeronaut. **11**:351, 1948; (*q*) Ricerche sugli effetti della associazione alcool-anossia sul senso luminoso, ibid. **11**:531, 1948. (*r*) Giardini, A., and Nižetić, B.: Ricerche sulla permeabilità della barriera ematooftalmica in rapporto all'anossia, Atti Soc. oftal. ital. **111**:444, 1949. (*s*) Giardini, A.: Faticabilità del meccanismo: Accomodazione-convergenza in anossia acuta, Riv. med. aeronaut. **12**:511, 1949. (*t*) Giardini, A., and Pisano, E.: Azione dell'ossigeno sul potere di fusione delle immagini retiniche, ibid. **14**:655, 1951. (*u*) Giardini, A.: Permeabilità della barriera ematooftalmica alla fluorescina in anossia acuta: (indagini sull'uomo), ibid. **15**:49, 1952. (*v*) Leonardi, F.: Sensibilità corneale in anossia acuta, ibid. **14**:416, 1951; (*w*) Gli effetti dell'inalazione de ossigeno sul meccanismo di accomodazione e convergenza, ibid. **14**:420, 1951. (*x*) Morone, G., and Citroni, M.: Indagini sugli intorbidamenti lenticolari da anossia: I. (*a'*) Condizioni di insorgenza della cosidetta catarata da anossia e suoi aspetti morfologici; (*b'*) Attività glicolitica anaerobica del cristallino in anossia; (*c'*) Influenza di condizioni varie sullo stato anossico della lente, ibid. **13**:655, 1950; II. ibid. **14**:464, 1951. (*y*) Nižetic, B., Jr.: Influenza dell'anossia sulla migrazione del pigmento retinico, ibid. **11**:516, 1948. (*z*) Scano, A.; Bietti, G. B., and Schupfer, F.: Influenza dell'anossia sul potere risolutivo retinico, ibid. **10**:490, 1947.

3. Mercier and Duguet.[1b] Giardini.[1v] Baertschi, W.: Physiologisch-pathologische Beobachtungen im Hohenflugzeug, Schweiz. med. Wchnschr. **60**:965, 1930.

4. McFarland, R. A., and Halperin, M. H.: Relation Between Foveal Visual Acuity and Illumination Under Reduced Oxygen Tension, J. Gen. Physiol. **23**:613, 1939-1940.

5. (*a*) Livingston, P. C.: Visual Problems of Aerial Warfare (Moyhihan Lectures), Lancet **2**:33, 1944. (*b*) Halstead, W. C.: Chronic Intermittent Anoxia and Impairment of Peripheral Vision, Science **101**:615, 1945; (*c*) Chronic Intermittent Anoxia and the Dynamic Visual Field, J. Psychol. **20**:49, 1945.

6. Boles Carenini and Brognoli.[2k] Ferraris de Gaspare and Boles Carenini.[2m] Goldmann, H., and Schubert, G.: Untersuchungen über das Gesichtsfeld bei herabgesztem Sauerstoffdruck der Atmungsluft, Arch. Augenh. **107**:216, 1933. Batenko, P. M., and Belostovskiy, E. M.: Effects of Altitude on the Blind Spot, Vestnik. oftal. **13**:816, 1938. Evans, J. N., and McFarland, R. A.: Effects of Oxygen Deprivation on the Central Visual Field, Am. J. Ophth. **21**:968, 1938. Seitz, C. P., and Rosenthal, C. M.: Effect of Oxygen Deprivation and Strychnine Administration on Visual Function: A Study of the Angioscotomas, Arch. Ophth. **26**:276, 1941.

7. (*a*) Boles Carenini and Brognoli.[2k] (*b*) Giardini.[2q] (*c*) Bunge, E.: Verlauf der Dunkeladaptation bei Sauerstoffmangel, Arch. Augenh. **110**:189, 1936. (*d*) Clamann, H. G.: Die Dunkeladaptationskurve des Auges bei Sauerstoffmangel, Luftfahrtmedizin **2**:223, 1937-1938. (*e*) Fischer, F. P., and Jongbloed, S.: Dark Adaptation of the Retina Under Oxygen Deficiency, Acta brev. neerland. **5**:182, 1935. (*f*) Livingston, P. C.: Studies on Night Vision and Night Visual Judgment as It Concerns the Ophthalmology of Flying, Irish J. M. Sc. **6**:177, 1942. (*g*) McDonald, R., and Adler, F. H.: Effect of Anoxemia on the Dark Adaptation of the Normal and Vitamin A-Deficient Subject, Arch. Ophth. **22**:980, 1939. (*h*) McFarland, R. A., and

(Footnotes continued on next page)

A reduction in the critical flicker fusion frequency, for both rods and cones,[9] and an increase in the latent period of positive after-images have been described.[10] The stereoscopic sense does not show any important change.[11] Strangely enough, the cornea shows a marked increase in sensitivity, both in chronic [12] and in acute [2y] anoxia.

Disturbances in Circulation and Fluid Exchange.—These are chiefly represented by a rise in the vascular pressure of the retina [13] and by a shifting of the color of the retinal arteries to a more violet tone, as observed with the ophthalmoscope.[13b] Moreover, acute anoxia increases the tension of the eye, the pressure quickly returning to normal as soon as a normal concentration of oxygen is reached again.[2e] In chronic anoxia modifications of the ocular tension are insignificant, but, according to some authors,[13c] a slight reduction of the intraocular pressure is met with. In this connection, an increased permeability of the blood-aqueous barrier has also to be remembered; this change is proved by the increased rate of diffusion of fluorescein into the anterior chamber when the dye is injected into the general circulation [14] and by the increased refractive index of the aqueous.[15]

Ocular Motility.—Among the effects of oxygen deficiency on this function, one notes, first, a slight exophthalmos,[16] due to sympathetic hyperexcitability. Pupil-

Evans, J. M.: Alterations in Dark Adaptation Under Reduced Oxygen Tension, Am. J. Physiol. **127**:37, 1939. (*i*) McFarland, R. A. and Forbes, W. H.: Effects of Variations in the Concentration of Oxygen and Glucose on Dark Adaptation, J. Gen. Physiol. **24**:69, 1940. (*j*) Posternak, J.: L'adaptation visuelle à l'obscurité au Jungfraujoch, Helvet. physiol. et pharmacol. acta **6**:516, 1948. (*k*) Wilmer, W. H., and Berens, C.: Medical Studies in Aviation: V. Effect et aptitude ñ la différentiation des couleurs, Compt. rend. Soc. biol. **138**:966, 1944.

8. (*a*) Boles Carenini and Cima.[2l] (*b*) Velhagen, K., Jr.: Die Hypoxämische Farbenasthenopie, eine latente Stöhrung des Farbensinnes, Arch. Augenh. **109**:605, 1936. (*c*) Fichter, H.: Über des Verhalten der normalen und anormalen Trichromasie bei Hypoxämie, Luftfahrtmedizin **5**:341, 1941. (*d*) Malmejac, G. L.; Ruffieux, R.; Chardon, G. ,and Serrell, E.: Anoxie et aptitude à la différentation des couleurs, Compt. rend. Soc. biol. **138**:966, 1944.

9. Seitz, C. P.: Effect of Anoxia on Visual Functions: A Study of Critical Frequency, Arch. Psychol. **36**:1, 1940. Bietti, G. B.; Grignolo, A., and Boles Carenini, B.: Comportamento della frequenza critica di fusione in condizioni di modificato apporto di ossigeno all'apparato visivo, Riv. med. aeronaut., to be published.

10. Gellhorn, E., and Spiesman, I. G.: Influence of Hyperpnea and of Variations of O_2- and CO_2-Tension in the Inspired Air upon After-Images, Am. J. Physiol. **112**:620, 1935. McFarland, R. A.; Hurvich, L. M., and Halperin, M. H.: Effect of Oxygen Deprivation on the Relation Between Stimula Intensity and the Latency of Visual After-Images, ibid. **140**:354, 1943.

11. Bunge.[3c] Clamann.[3d] Heinke, E.: Raumsehen im Unterdruck, Luftfahrtmedizin **2–3**: 174, 1942. Duguet, J.: Le comportement de la parallaxe stéréoscopique en anoxie, Méd. aéronaut. **2**:36, 1947.

12. Zwahlen, P., and Grandjean, E.: Variation des sensibilités cornéenne et cutanée à l'altitude, Helvet. physiol. et pharmacol. acta **6**:471, 1948.

13. (*a*) Bietti and Lo Monaco-Croce.[2e] (*b*) Duguet, J.; Dumont, P., and Bailliart, J. P.: Action de l'anoxémie et de l'inhalation d'oxygen sur la circulation rétinienne, La Méd. aéronaut **2**:201, 1947. (*c*) Grandjean, E., and Zwahlen, P.: Modifications de l'ophtalmotomus et de la préssion artérielle rétinienne en haute montagne, Helvet. physiol. et pharmacol. acta **6**:560, 1948.

14. Giardini and Nižetić.[2r] Giardini.[2n] Giardini, A., and Swanljung, H.: Effects of Anoxia on Fluorescein Permeability of the Blood-Aqueous Barrier, Brit. J. Ophth. **35**:114, 1951.

15. Bellows, J., and Nelson, D.: Cataract Produced by Anoxia, Arch. Ophth. **31**:250, 1944.

16. Wiesinger, K.: Untersuchungen über die Bulbuslagen in der Orbita, Helvet. physiol. et pharmacol. acta **6**:617, 1948.

lary changes are also met with, according to studies by Scano and me.[2d] These changes consist of an increased size of the pupil, accompanied by increased speed of contraction and decontraction with adequate stimulation; anisocoria, and reduction in the intensity and duration of miosis with light stimuli. With very low illumination and in severe anoxia the pupil may become unexcitable and may escape the well-known effects of an acoustic collateral stimulation (psychic restitution effect, Loewenstein). An increase in the fatigability for both pure accommodation and accommodation plus convergence is found, owing to displacement of the near point, at high altitudes.[17] In anoxic conditions the ocular-muscle balance is interfered with, and even if there is no agreement about the type of changes, the cases in which heterophoria appears or an existing one is modified are very frequent.[18] In my experience, there is a general tendency toward esophoria, which is more pronounced for distance. A deficiency of the convergence in near vision, as well as slight vertical heterophoria,[2f] is also found. In severe anoxia the amplitudes of convergence and divergence are reduced.[2g] Anoxia interferes with voluntary coordinate ocular movements: The reading time is prolonged, partly owing to a reduction of attention, but mainly because the movements of the eyes are slower; combined with this effect are an increase in the required number of fixations and a more frequent swinging back to groups of figures previously misjudged.[19] Finally, in anoxia an enlargement in the width of the palpebral fissure and an increase in the blinking rate are found.[2b,d]

Changes in Transparency of the Ocular Media.—Aside from the increase in the refractive index of the aqueous humor already mentioned these changes consist in opacities of the lens, which disappear as soon as normal oxygen concentration is restored.[20] It must be recalled, however, that these opacities are found only in experimental animals in a condition of severe anoxia.

Present Investigation

It is of interest to note that all the above-mentioned changes have been noted in normal subjects and that only exceptionally have students of aviation medicine tested the behavior of the ocular functions in morbid conditions under lack of oxygen. As far as I know, it has been observed only that some heterophorias increase under lack of oxygen, to the extent of diplopia,[18d] and, according to others (Velhagen[5b]), that some dischromatopsic conditions became worse when tested during anoxia, but even on the last point there is still debate (Fichter[8c]).

My attention was drawn, therefore, to the behavior in some abnormal conditions, since preliminary researches had indicated to me that such an investigation would be of particular interest not only for the special purposes of aviation medicine but

17. Mercier and Duguet.[1b] Livingston.[5a] Wilmer and Berens.[7k]

18. (*a*) McFarland, Evans, and Halperin.[1a] (*b*) Mercier and Duguet.[1b] (*c*) Wilmer and Berens.[7k] (*d*) Sauer, W.: Effects of Altitude on the Eyes of Aviators and Observers (and comment by Weldon), Ohio M. J. **20**:629, 1924. (*e*) Scobee, R. G.: Effect of Exhaustion and Moderate Anoxia on Ocular Muscle Balance, U. S. Air Force School Aviat. Med., Randolph Field, Proj. 292, Res. Rep. 1, July 18, 1944. (*f*) Adler, F. H.: Effect of Anoxia on Heterophoria and Its Analogy with Convergent Concomitant Squint, Arch. Ophth. **34**:227, 1944.

19. Bietti and Scano.[2b] McFarland, R. A.; Knehr, C., and Berens, C.: Effects of Oxygen Deprivation on Eye Movements in Reading, J. Exper. Psychol. **21**:1, 1937.

20. Bellows and Nelson.[15] Morone and Citroni.[2k]

more especially for clinical ophthalmology. In effect, anoxia had revealed itself capable of uncovering latent pathologic conditions the detection of which was of the greatest value in declaring some subjects unfit for flying activities, and especially in recognizing some ocular diseases which were in an early phase, and not evident in the regular examination of the patient.

In our investigations my collaborators and I obtained anoxia by letting the patient breathe for at least 10 minutes an oxygen-poor mixture reproducing the conditions met in the normal atmosphere between 13,000 and 26,000 ft. (3,900 and 7,800 meters). The breathing of the mixture was usually interrupted as soon as general difficulties appeared or the patient's attention was reduced. During anoxia the visual fields were checked routinely. In particular cases we also determined the central visual acuity and tested the extrinsic ocular motility with the usual means (Maddox cross and rod, Hess coordimeter). The visual field was explored, particularly in its central portion, with a tangent screen at 2 meters and constant diffuse illumination of moderate intensity. Owing to the difficulty of establishing the limits in the variations of the light sense caused by reducing the oxygen supply in normal and in pathologic subjects, this aspect of the ocular function was not tested in our patients. The same difficulty, but to a slighter degree, was found when the central visual acuity was tested. That was a case, too, for the reduction in the peripheral limits of the visual field for white and colored objects which is produced by lack of oxygen; only extreme contractions, especially in a given area, were considered. On the contrary, there was no difficulty of interpretation when a central or paracentral scotoma appeared, when deep notching of the peripheral visual field was observed, or when a preexisting defect of the visual field became noticeably enlarged. It should be emphasized that only an evident enlargement of a previously seen area of scotoma, or the appearance of new ones, can be considered of value in the diagnosis of a latent pathologic condition when tested under oxygen deficiency. A slight increase in size, up to 1 or 2 degrees, of a preexisting large scotoma might be attributed exclusively to the increased "retinal inertia" (Goldmann[21]) of the healthy zones of the retina, whose function is depressed by reduced oxygen supply; consequently, such an increase is devoid of any pathologic significance.

A reduction of the oxygen content of the eye and its appendages may be brought about not only by having the patient breathe an oxygen-poor mixture or by putting him in a depression chamber, but also by inducing any one of the following conditions: apnea, vasoconstriction, head-seat acceleration, and compression of the eyeball. In the last condition, however, it must be noted that compression is effective only upon the retina itself and the lower, peripheral part of the visual pathways, in any case not beyond the third neurone. In my studies I used routinely only the last of the above-mentioned methods. The compression of the eyeball was obtained with an ophthalmodynamometer of the Bailliart type[22] (Fig. 1). The instrument was placed on the temporal side of the eyeball, and the retinal arterial pressure was first measured; the pressure was then sufficiently increased to overcome the retinal diastolic pressure, of 15 to 30 gm. The time of compression was never extended beyond 10 minutes. All examinations were carried out while the compression was maintained.

21. Goldmann, H.: Beitrag zur Angioskotometrie, Ophthalmologica **114**:147, 277, 1947.

22. Other dynamometers, e. g., the dynamometer of H. K. Müller, may be used.

It has long been known that compression of the eyeball causes ischemia, which, if severe, may lead to sudden amaurosis. But I am not concerned here with such severe compression. I should like, however, to note some effects of moderate compression, which previously have received little attention (Bailliart,[23] Evans,[24] Andina,[25] Bietti and Scano,[26] Goldmann,[21] Cibis and Hochgeschürz,[26] Best and von Glasenapp[27]). Moderate compression, with the pressure just above the retinal diastolic pressure, and in any case not beyond the intermediate value between the diastolic and the systolic retinal pressure, is likely to produce a slight concentric contraction of the visual field (owing, at least partly, to a general depression of the retinal sensibility and, consequently, to an increase in the "inertia" phenomena), and impairment of the light sense. In general, it does not interfere with the central portion of the visual field; that is, the blind spot is only moderately increased under compression, and a central or paracentral scotoma does not appear in subjects with a normal visual organ. It should be emphasized that, while the behavior of a

Fig. 1.—Bailliart's ophthalmodynamometer to measure the pressure of the retinal arteries and to exert a graded compression on the eyeball in order that the oxygen supply to the retina and optic nerve may be reduced.

normal eye when compressed is rather well defined, very little is yet known about the functions of a pathologic eye under dynamometric compression. As far as I know,

23. Bailliart, P.: Circulation artérielle rétinienne: Essais de détermination de la tension dans l'artére centrale de la rétine, Ann. ocul. **154**:257, 1917.

24. Evans, J. N.: Introduction to Clinical Scotometry, New Haven, Conn., Yale University Press, 1938; Sorsby, A., Editor: Modern Trends in Ophthalmology, Ed. 2, New York, Paul B. Hoeber, Inc., 1948, Vol. 2, p. 141.

25. Andina, F.: Über Schwarzsehen als Ausdruck von Blutdruckschwankungen bei Sturzflugen, Schweiz. med. Wchnschr. **67**:753, 1937.

26. Cibis, P., and Hochgeschürz, G.: Experimentelle Untersuchungen über die Wirkung der durch künstliche Steigerung des intraokularen Druckes hervorgerufene Ischämie auf die Funktion der Netzhaut, von Graefes Arch. Ophth. **148**:752, 1948.

27. Best, W., and von Glasenapp, I.: Über die Wirkung kurzdauernder experimenteller Steigerung des i. o. Druckes auf die Netzhautfunktion, Ber. Versamml. deutsch. ophth. Gesellsch. **55**:232, 1949.

there are only the studies of Wegner [28] and Samojloff [29] in cases of glaucoma and optic nerve atrophy, but their findings are incomplete and contradictory. With our technique, compression of the eyeball produces the same result as anoxia with respect to peripheral lesions. An indirect demonstration of this may be seen in the fact that the impairment of the light sense (Best and von Glasenapp [27]), (Nižetić [30]), the enlargement of the blind spot (Bietti [31]), and the impairment of the color sense (Boles Carenini and Cima [21]), when induced by compression, are immediately relieved by inhalation of pure oxygen at atmospheric pressure.

I should like to point out that ischemia and anoxia are not the same thing, since in the former, besides the reduction in oxygen supply of the tissues, stasis phenomena and lack of other nutritional substances play a role, whereas in the latter the only factor is lack of oxygen. It is interesting, however, to note that, for purposes of clinical diagnosis, compression and induction of anoxia give identical responses regarding the retinal function. Therefore, with particular exceptions, the compression of the eyeball may be used to replace anoxia, and this as long as the intraocular circulation is tested. For ophthalmologists who are not especially equipped for the anoxia test, the practical advantage of such a method is evident.

Experimental Results.—The diseases represented by the patients examined were lesions of the optic nerve and the optic pathways; chorioretinal changes, such as inflammation, degenerative conditions, detachment of the retina, and vascular diseases; glaucoma; anomalies of the ocular motility, and suppression amblyopia in strabismus. Patients with early, well-developed, and old lesions were tested. The results of this study are of interest, as they revealed functional deficiencies which cannot be found in the normal eye, and which cannot be detected by routine examination, including reduced illumination and use of small test objects, in the diseased eye. The most striking features noted under anoxia or moderate compression of the eye were marked contraction of the visual field in some areas, appearance of scotomata or enlargement of previous existing ones, and marked lowering of visual acuity.

All disturbances due to anoxia or ischemia rapidly disappeared when pressure was released or the oxygen supply was restored to normal levels.

Glaucoma: In the glaucomatous eye enlargement of the existing scotoma was generally striking, so that sometimes visual field changes of a more advanced stage of the disease were brought into evidence. But a real diagnostic clue was found in very early stages of chronic glaucoma. At this stage, when the blind spot was still normal in size, a marked enlargement at its superior and inferior poles was induced by anoxia or ocular compression. As I reported at the Sixteenth International Ophthalmological Congress, in London,[31] the anoxia test is a new and additional method for the early diagnosis of chronic simple glaucoma (Fig. 3). Another

28. Wegner, W.: Kann Skotombildung allein durch Erhöhung des intraokularen Druckes bedingt sein? Ztschr. Augenh. **56**:48, 1925.

29. Samojloff, A.: Weitere Untersuchungen über die Skotombildung, Ztschr. Augenh. **58**:282, 1926.

30. Nižetić, B., Jr.: Del portere di ripristino esercitato da alcune sostanze sull'abbassamento del senso luminoso provocato dalla compressione sperimentale del globo oculare, Atti Soc. oftal. ital. **11**:492, 1949.

31. Bietti, G. B.: Di un nuovo test per la diagnosi precoce del glaucoma, Acta XVI Conc. Ophth., London **2**:895, 1950.

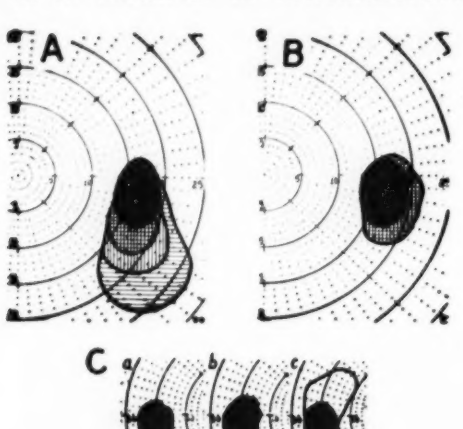

Fig. 2.—Pathologic (*A*) and normal (*B*) enlargement of the blind spot (object, 5/2000 white) under a compression pressure of 80 gm. (diastolic retinal pressure 50 gm.; ocular tension 30 to 28 mm. Hg). The greatest limit appeared after 10 minutes. *C*, blind spot (object, 3/2000 white) after successful trephining operation for chronic simple glaucoma: (*a*) before tests; (*b*) after lability and water-drinking test (this and similar provocative tests give marked enlargement of the blind spot only before the operation); (*c*) after 10 minutes of anoxia at 13,200 ft (continuous line).

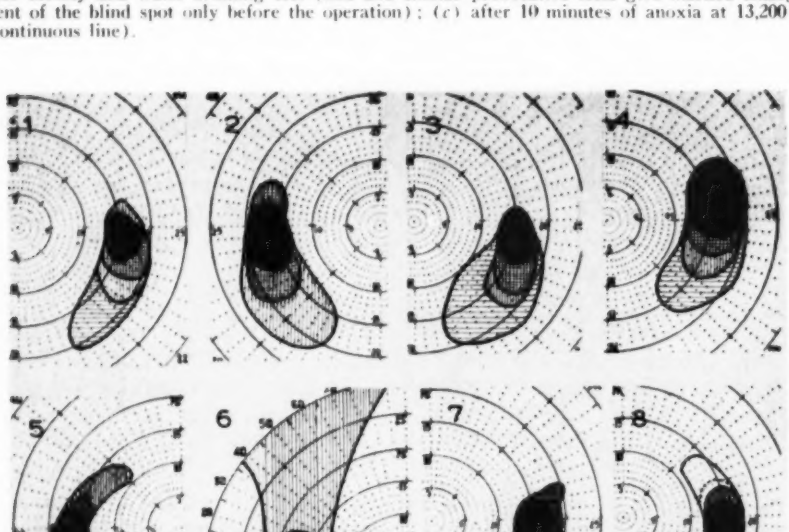

Fig. 3.—Examples of enlargement of the blind spot (objects, 3/2000 or 5/2000 white) in early glaucoma after different periods (generally 2 minutes; extremes 5 to 10 minutes) of compression (from 60 to 100 gm.) of the eyeball. In every patient the intraocular pressure was below 30 mm. Hg; vision and visual fields were normal with small objects at low illumination. In Case 8 the greatest extension was reached after 5 minutes, becoming smaller at 10 minutes (dotted line). It is to be noted that the reaction of the blind spot to compression may be different on different days. Fairly similar results could be obtained by anoxia.

feature of the glaucomatous eye was the rapid return to normal of the enlarged blind spot when the compression pressure was released, but within 10 to 15 minutes it again became enlarged, even to the size that was reached during the compression test. In eyes in which a fistulization had previously been performed, the anoxia test proved to be the only means of making a diagnosis in retrospect. In such eyes the compression test was not performed because it seemed too dangerous. It may be noted that anoxia corresponding to 16,500 ft. (5,000 meters), with about 10% of oxygen in the inspired mixture, induced in glaucomatous subjects, even those who still had a normal audiogram, a fall in the sensitivity to high tones (4000 to

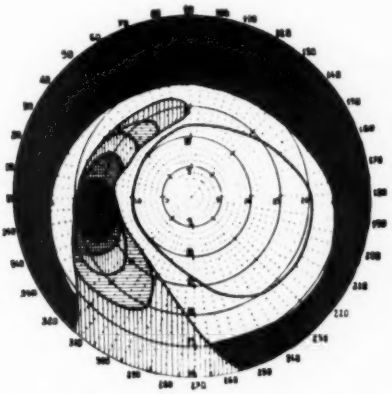

Fig. 4.—Enlargement of the blind spot (object, 3/2000 white) and "baring" of it by the isopters for 1/2000 white after compression of the eyeball (80 gm.) for 2 to 10 minutes.

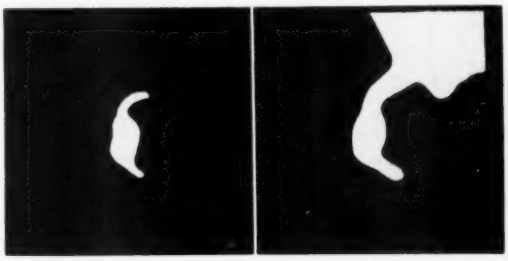

Fig. 5.—Angioscotometric determinations (object, 0.3/190 white) in early chronic glaucoma, before (left) and after (right) 10 minutes of 60-gm. compression (diastolic pressure of retinal arteries, 45 gm.). A wedge-shaped defect appears.

8000 cycles). These auditory changes are similar to those in glaucomatous patients with impairment of hearing and to the acoustic findings in glaucomatous patients after provocative tests, in which the intraocular pressure is artificially raised, as I have demonstrated with my co-workers Ferraris de Gaspare and Maffei.[20] In the normal subject, as well as in patients with vascular deafness or presbycusis, an anoxia corresponding to the aforementioned altitude of 16,500 ft. induced no, or only slight, changes in the audiogram. Trouble was seen only when anoxia was pushed to altitudes of 23,000 to 26,000 ft. (7000 to 7800 meters), but even in this case the changes never reached more than 10 db. of amplitude.

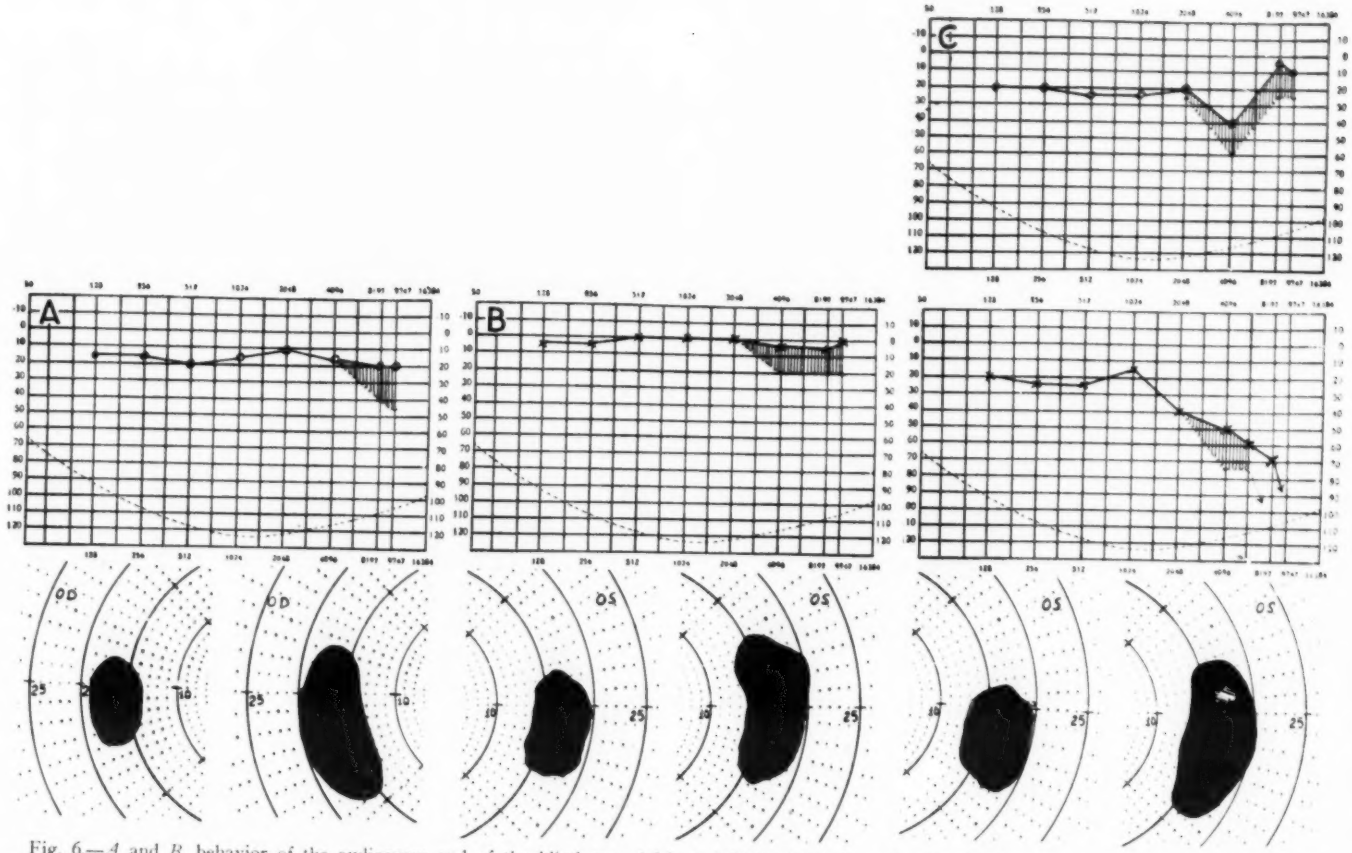

Fig. 6.—*A* and *B*, behavior of the audiogram and of the blind spot (object, 3/2000 white) in early chronic glaucoma during anoxia (16,500 ft. for 10 minutes). The still-normal audiogram at sea level is impaired during anoxia (at high frequencies), the changes paralleling the enlargement of the blind spot. *C*, typical audiograms for a patient with chronic glaucoma further impaired by anoxia (16,500 ft. for 10 minutes). The changes parallel the enlargement of the blind spot (object, 3/2000 white).

Optic Neuritis: Anoxia produced enlargement of a preexisting scotoma and the enlargement of previous defects in the visual field in optic neuritis. In some cases of initial or overlooked retrobulbar neuritis the anoxia or compression test allowed me to find a central or centrocecal scotoma with noticeable loss of visual acuity. Incidentally, I have differentiated choked disk and beginning optic neuritis with the help of the anoxia test.

Miscellaneous Diseases of Retina and Choroid: In retinal detachment anoxia did not increase the defect of the visual field, except when recovery had already occurred. In such cases, again, as in the eye operated on for glaucoma, we did

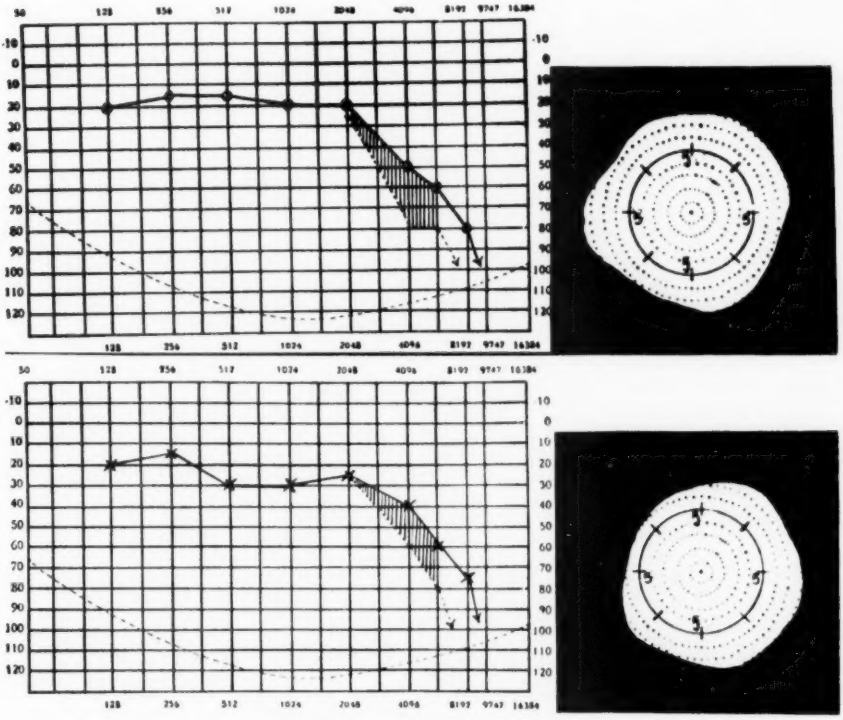

Fig. 7.—Effect of anoxia in impairing the audiogram and narrowing the visual field in a case of glaucoma.

not perform the compression test, as such a technique seemed to involve too much danger for the patient.

Lesions of the Optic Pathways: The behavior of such lesions is of particular interest. In such a condition anoxia may reduce the visual field, to produce, for instance, the picture of a quadrantic hemianopsia. It should be recalled that, while anoxia as obtained by having the subject breathe an oxygen-poor mixture, or by placing him in a depression chamber, may reveal lesions beyond the primary optic centers, as well as those in the first three neurones, compression of the eyeball cannot reach any lesion beyond the third neurone. By using anoxia or compression

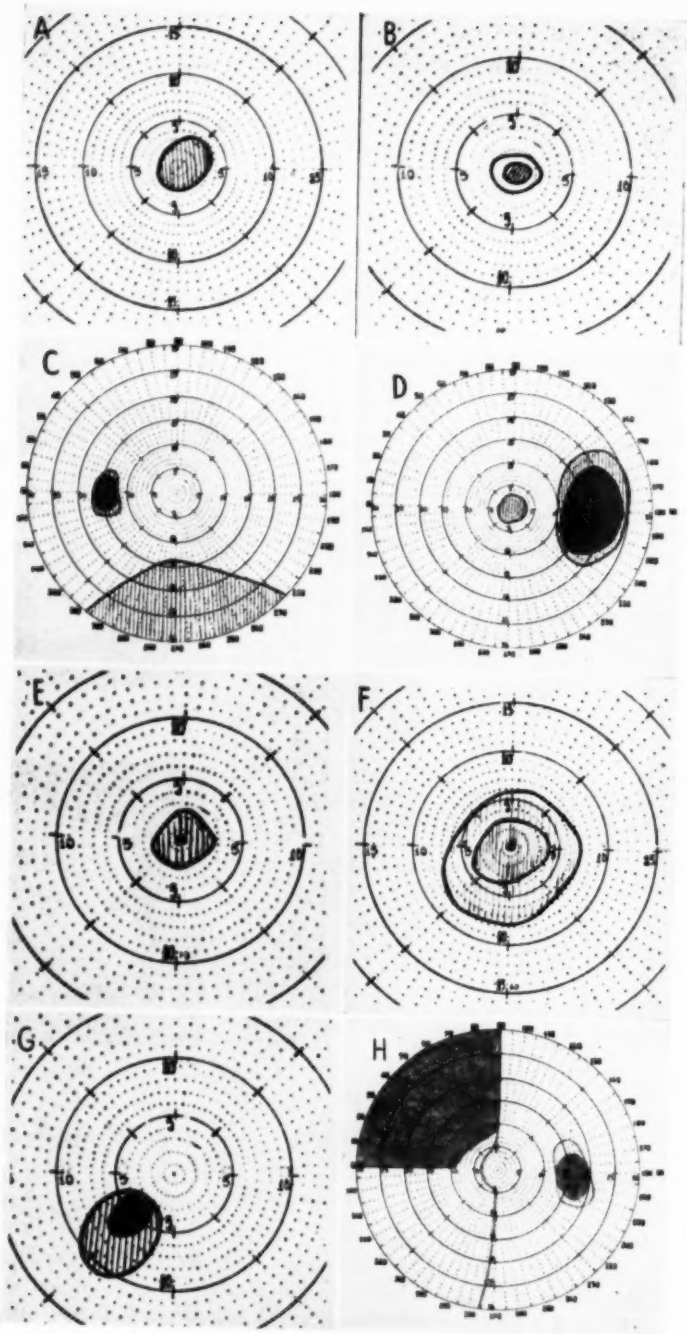

Figure 8

(See legends on opposite page)

of the eye, one has, therefore, the possibility of determining the level of a lesion along the optic pathways. This diagnostic procedure has already proved to be of some value. It is interesting to point out that compression of the eyeball may also bring into evidence lesions of the retina and of the third neurone, even if a disturbance of the latter is located outside the bed of the central retinal artery (for instance, the optic chiasm or the optic tract). This is apparently because the lower portion of the third neurone (the portion whose oxygen supply can be reduced by local compression) becomes involved in lesions of its higher portion, even at an early stage.

For localization of a lesion along the optic pathways, one must be sure that the changes seen in the visual field are not due simply to the increased "inertia" in the still healthy retina in connection with a depression of its activity owing to the oxygen lack. As has been pointed out, a reduction of 1 or 2 degrees in the limits of the visual field under reduced oxygen supply cannot be considered pathologic,

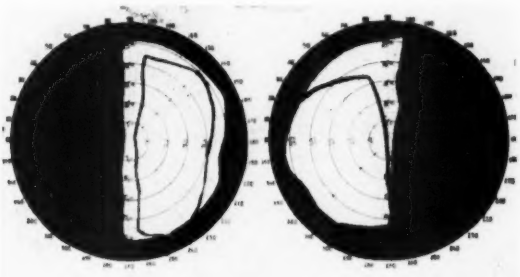

Fig. 9.—Bitemporal hemianopsia in a case of lesion of the chiasm. The visual field was contracted and the central vision lowered during both anoxia (16,500 ft.) and compression (60 gm.) of the eye for five minutes (object, 2/2000 white), in connection with the low site of the lesion.

unless new scotomata appear. In these studies only the positive results should be considered in the localization. Negative results, in which a reduced oxygen supply does not show any increase in the visual field defects, cannot be taken into account

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Explanation of Figure 8

Fig. 8.—*A*, toxic amblyopia at onset, with normal vision. Compression of the eyeball (80 gm.) and anoxia (19,800 ft., 6,000 meters) provoked the appearance of a central scotoma (object, 1/2000 white). *B*, cured toxic amblyopia, with normal vision. Anoxia (25,000 ft., or 7,500 meters) and compression of the eyeball (80 gm.) revealed, again, a central scotoma (object, 1/2000 white; outer line shows scotoma for compression). *C*, segmental optic neuritis. Compression (70 gm.) of the eyeball for three minutes showed a large defect in the lower part of the visual field (object, 3/2000 white). *D*, papillitis, with nearly normal vision. Compression (60 gm. for three minutes) re caled, through the appearance of a central scotoma, the impairment of the papillomacular bundle (object, 1/2000 white). *E*, beginning macular degeneration. Enlargement of a tiny central scotoma occurred through anoxia (16,500 ft.) or compression of the eyeball (70 gm.) for a few minutes (object, 1/2000 white). *F*, central chorioretinitis. A tiny scotoma became enlarged during five minutes of anoxia (16,500 ft.) and even more (outer line) through compression of 70 gm. (object, 1/2000 white). *G*, thrombosis of cilioretinal arterioles (syphilitic). A paracentral scotoma was enlarged under anoxia (16,500 ft.) and compression of the eye (70 gm.) for four minutes (object, 1/2000 white). *H*, homonymous upper-quadrant hemianopsia of vascular origin. Anoxia (23,100 ft. for 10 minutes) produced impairment of the lower quadrant also (object, white, 1/2000). There was no change with compression of the eyeball because of the high location of the lesion.

for purposes of localization, owing to the fact that lack of changes in the visual field under anoxia or compression of the eyeball may also be the expression of sharply circumscribed lesions, without partial involvement of neighboring areas to be brought in evidence through oxygen deficiency.

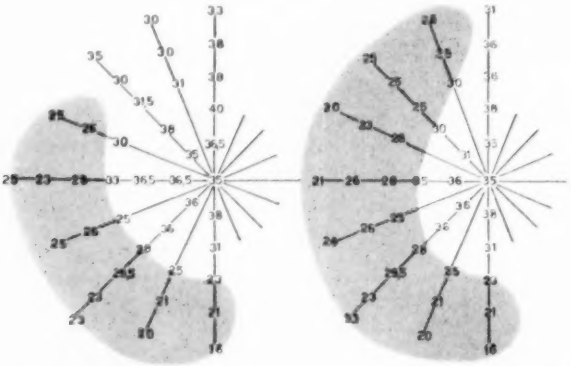

Fig. 10.—Flicker fusion frequency after improvement in the field shown in Figure 8 while the patient was breathing normal air and during anoxia (16,500 ft. for five minutes). Anoxia produced impairment of the lower quadrant also.

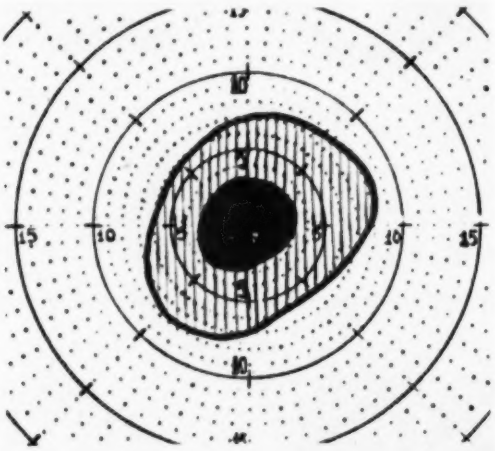

Fig. 11.—Central scotoma in strabismus with amblyopia which became enlarged both during anoxia (16,500 ft. for five minutes) and compression (60 gm.) of the eye (object, 2/2000 white), showing that the effects of suppression phenomena reached the lower part of the optic pathway.

Critical Flicker Fusion Frequency: Sometimes this finding is much more sensitive to anoxia than is the visual field. For instance, in a case of quadrantic hemianopsia (Fig. 8*H*), after improvement of the lesions it was no longer possible to discover during anoxia any defect of the lower quadrants of the visual field. With the flicker fusion frequency test, however, it was possible to demonstrate that in

anoxia the lower right quadrants were no longer reacting normally, as during the breathing of normal air.

Suppression Scotomata in Strabismus with Amblyopia: It is also interesting to recall that enlargement of the suppression scotomata in strabismus with amblyopia may be elicited both by anoxia and by compression of the eyeball. One is therefore led to believe that the processes of suppression in strabismus, even if of cortical origin, reach the retina when amblyopia is present, and are thus more widespread than was previously thought.

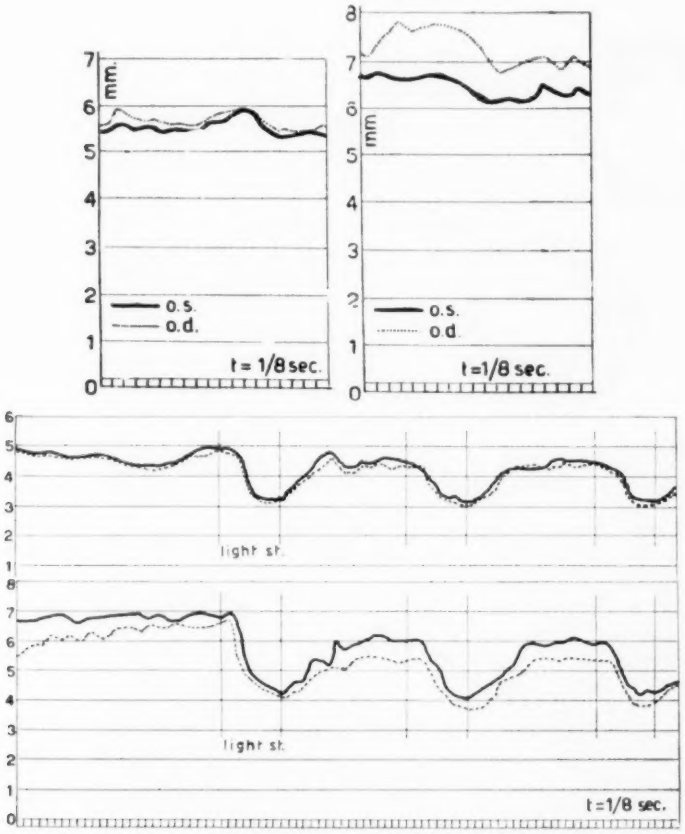

Fig. 12.—Above: Pupillographic tracing of spontaneous rhythm in darkness while the patient was breathing normal air (left) and during anoxia (right) at 24,800 ft. (7,500 meters) for eight minutes. Both pupils became enlarged, but mydriasis was more pronounced for the right eye.

Below: Pupillographic tracing showing that the anisocoria produced by anoxia (20,150 ft., or 6,000 meters for nine minutes) became reduced during the photomotor reflex, that is, during parasympathetic contraction.

It should not be forgotten that if the compression of the eyeball is too slight or the duration too short, the scotoma may disappear or contract, at least at the beginning, while an enlargement of the scotoma occurs afterward with a rise in the

applied pressure or the prolongation in the time of compression. This temporary improvement in the functional condition is chiefly to be attributed to a slight degree of congestion, which brings about an increased utilization of oxygen. This view is substantiated by the finding that inhalation of oxygen or vasodilation (as a means of increasing the oxygen supply to the ocular tissues) permitted some scotomata to disappear, or at least reduced them in size.

Ocular Motility: This function is interfered with by general anoxia, so that heterophorias, muscular paresis, and nystagmus may appear or be aggravated during an anoxia test. A lack of oxygen, obvious as obtained by the general inhalation

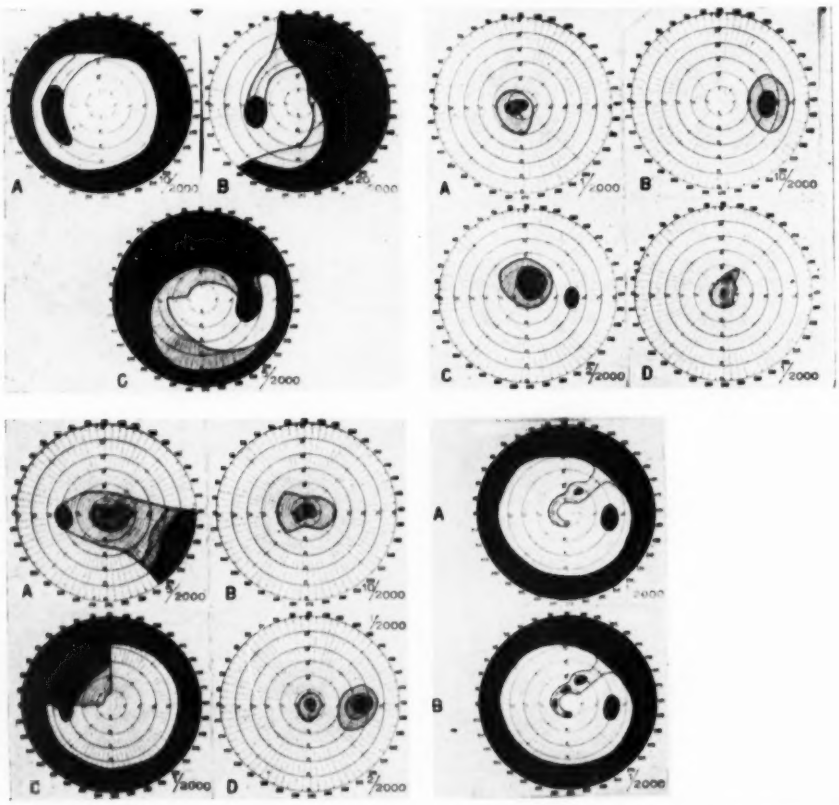

Fig. 13.—Upper left: Visual fields in chronic glaucoma, before and after 5 to 10 minutes of oxygen inhalation. *A* and *B* are fields in nonsurgical cases; *C*, a field in a case after operation.

Upper right: *A*, toxic amblyopia; blind spot before and after 5 and 10 minutes of oxygen inhalation. *B*, choked disk; blind spot before and after 10 minutes of oxygen inhalation. *C*, old toxoplasmosis; blind spot before and after 10 minutes of oxygen inhalation. *D*, Stargardt's macular degeneration, blind spot before and after 10 minutes of oxygen inhalation.

Lower left: *A*, neuroretinal atrophy following arterial spasm; blind spot before and after 5 and 10 minutes of oxygen inhalation. *B*, old central post-traumatic chorioretinitis; blind spot before and after 5 and 10 minutes of oxygen inhalation. *C*, quadrantic hemianopsia due to cortical lesion; blind spot before and after two minutes of oxygen inhalation. *D*, suppression scotomata in strabismus before and after 5 and 10 minutes of oxygen inhalation.

Lower right: Old perimacular lesions of doubtful origin: *A*, before and after 10 minutes of oxygen inhalation; *B*, before and after four daily subconjunctival injections of oxygen.

method, may bring into evidence a difference between the neurovegetative tone of the two sides of the body which was not apparent under normal conditions. This happened in the case of the pupillographic tracing obtained with Loewenstein's technique (Fig. 12); in this case the two pupils were dilated to different degrees under anoxia, while before the test they were isocoric. Sometimes, when the pupils contract to light, such a stimulated anisocoria disappears, so that one might infer that the anisocoria was of sympathetic origin. In other cases anisocoria becomes evident only during the contraction of the pupils, indicating that it is of parasympathetic origin.

Comment.—From this review of the effects of the reduced oxygen supply on the retina, as well as on the muscular and nerve tissues of ophthalmic interest, it

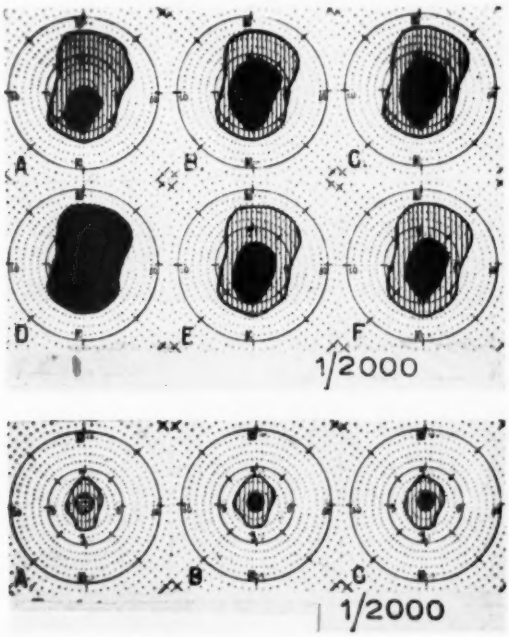

Fig. 14.—Above: Central scotoma in toxic amblyopia before and after (*A*) 10 minutes of oxygen inhalation; (*B*) three daily subconjunctival injections of 3 cc. of oxygen; (*C*) three daily subconjunctival injections of 3 cc. of nitrogen; (*E*) after inhalation of 4 drops of amyl nitrite; (*F*) after intravenous injections of 30 mg. of nicotinic acid.

Below: Central scotoma in macular chorioretinitis before and after (*A*) 3 and 10 minutes of oxygen inhalation (the scotoma has completely disappeared); (*B*) inhalation of 4 drops of amyl nitrite; (*C*) intravenous injection of 30 mg. of nicotinic acid.

becomes evident that an oxygen deficiency not only is responsible for changes in physiologic conditions, and in some permanent ocular lesions (mainly, glaucoma and vascular disease), but is also of great interest in revealing certain subclinical or latent changes which usually escape in the routine examination, and the anoxia test becomes, therefore, an additional diagnostic and prognostic procedure in the field of ocular diseases. My investigations prove, moreover, that the action of anoxia in the visual functions may be both peripheral and central.

HYPEROXIA

Hyperoxia, obtained chiefly through inhalation of pure oxygen at atmospheric pressure, should be briefly considered, as it has an action in some pathologic conditions of the eyes and might be used for clinical purposes.

In previous reports [32] attention was called to the favorable influence of inhalation of pure oxygen on some ocular functions, not so much in improving the normal

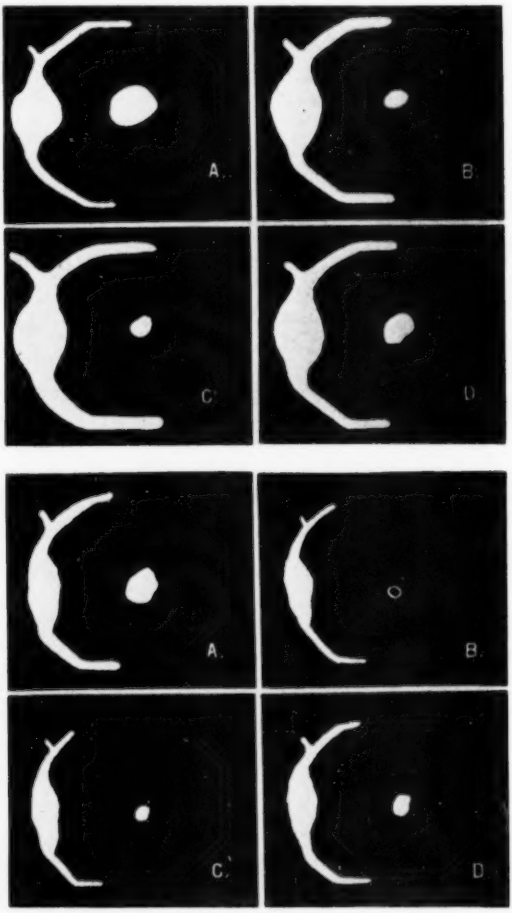

Fig. 15.—Above: Toxic amblyopia: Behavior of the central scotoma and of the angioscotoma (*A*) before treatment; (*B*) after 10 minutes of oxygen inhalation; (*C*) after inhalation of 4 drops of amyl nitrite; (*D*) after intravenous injection of 30 mg. of nicotinic acid. In this case the central scotoma was reduced, but the angioscotoma was enlarged, especially with amyl nitrite.

Below: Suppression scotoma (amblyopic eye) in strabismus (*A*) before treatment; (*B*) 5 to 10 minutes after inhalation of oxygen; (*C*) after inhalation of amyl nitrite; (*D*) after intravenous injection of 30 mg. of nicotinic acid. Both the central scotoma and the angioscotoma were reduced in this case. In *B* the central scotoma had even disappeared after 10 minutes.

32. Bietti and Ferraris de Gaspare.[2b] Bietti, footnotes *2 i* and *j*.

ones as in restoring functions that have been modified by pathologic conditions or by simple fatigue.

Moreover, I have already stated that the inhalation of oxygen reduces or eliminates the effects of moderate compression of the eyeball, performed according to the aforementioned technique. Even if the responses of diseased eyes to the increased oxygen supply were not uniform, the results were comparatively better in some conditions. The inhalation of oxygen was particularly likely to result in enlargement of the affected visual field in glaucoma, and to reduce the size of the enlarged blind spot and other typical scotomata both when the intraocular pressure

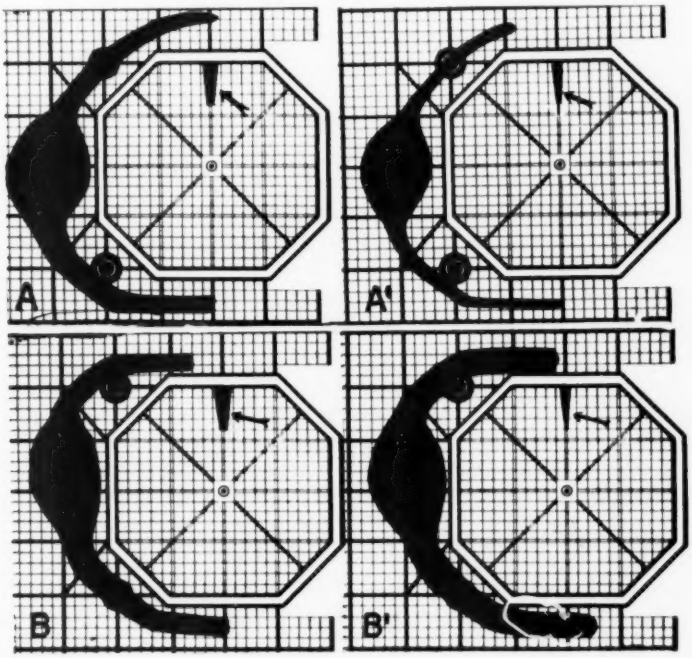

Fig. 16.—Angioscotoma and "Goldmann's slit" before and after 10 minutes of oxygen inhalation. In the first case (*A*) and (*A'*) both the "slit" and the angioscotoma are reduced in size (commoner occurrence); in the second (*B*) and (*B'*) the "slit" appears reduced, but the angioscotoma is enlarged.

was high and when it was normalized by antiglaucoma operations. Good effects on the visual field were observed in several active, or already inactive, diseases of the optic nerve, as well as in retinal and choroidal inflammations and degenerations. A similar effect occurred in suppression scotomata of amblyopic eyes.

Less pronounced, or even absent, was the effect of the increased oxygen supply on the visual field in retinal detachment, in retinal thrombosis, and in fundus changes in myopia. An improvement of the visual field was also seen in some hemianoptic lesions of central origin. Much the same results could be obtained through hyperventilation, as well as by injecting nicotinic acid intravenously or by

breathing amyl nitrite. Thus, the action of these substances on the retinal functions is connected with an increased oxygen supply to the visual apparatus.

Features common to the various diseases in the patients examined were that the enlargement of the visual field and the contraction of the scotomatous areas ceased after a few minutes of oxygen inhalation without any further increase occurring, and that the return to ordinary air breathing was rapidly followed by the reestablishment of the original capimetric conditions; there was no constant relation between the improvement of the ocular function obtained through oxygen inhalation and the age of the lesion.

I also examined the behavior of the normal angioscotoma during oxygen inhalation. In contrast to the previous findings of Rosenthal,[33] who reported a constant contraction under oxygen intake, and Duguet and collaborators,[34] who saw always a dilatation, we found a contraction of the angioscotoma in 80% of cases and an enlargement in 20%. Pathologic scotomata, not connected with the vascular shadow, if present in the same subject, never reacted to oxygen inhalation with enlargement, but were always reduced or unmodified. This suggested that in the changes of the angioscotoma two factors may be involved: an increase or a decrease in retinal sensitivity, and modifications in the width of the vessels.

To study this point, I made some investigations, especially with my assistant Ferraris de Gaspare,[2b] by using the so-called artificial angioscotoma, or "slit of Goldmann,[21]" under both reduced and increased oxygen supply. Goldmann showed that if a vertical slit 5 cm. long and 5 mm. wide, made in a cardboard (covered with oil paper and illuminated from behind), was held 60 cm. from the observer and a point some 7 cm. below the lower end of the slit was fixed, then a small (2 mm.) light source, as in the Maggiore perimeter, projected on the board moved laterally toward the slit would become invisible when the slit was reached, provided there was little contrast between the illumination of the slit and that of the projected object. The spot reappeared when it had passed beyond the other edge of the slit. The width of the interval of disappearance of the spot could be exactly measured on the board and appeared to become smaller or larger according to the conditions of the retinal functions. Goldmann did not, however, perform any simultaneous examination of the behavior of the slit and that of the angioscotoma, and this is what we did, using the same board.

We saw, thus, that the increased oxygen supply (oxygen inhalation or administration of vasodilators) was regularly followed by a reduction in the diameter of the slit, while anoxia or the administration of vasoconstrictors was followed by its enlargement, all this independently of the behavior of the angioscotoma, which did not parallel the behavior of the slit. This proves that examination with the Goldmann slit gives much more exact information on the retinal sensitivity than does angioscotometry, in which the increased or decreased sensitivity may be interfered with by the vasodilatation or vasocontriction. Changes in diameter of the retinal vessels may thus be followed by an enlargement of the angioscotoma even when the retinal

33. Rosenthal, C. M.: Changes in Angioscotomas Associated with Inhalation of Oxygen, Arch. Ophth. **22**:385, 1939.

34. Duguet, J.: Dumont, P., and Bailliart, J. P.: Action de l'anoxémie et de l'inhalation d'oxygène sur la circulation retinienne, Méd. aeronaut. **2**:201, 1947.

function is improved (as by the giving of vasodilators) or by a reduction in the size of the angioscotoma even when the retinal sensitivity decreases (as with vasoconstriction) if the vascular component prevails. I have discussed elsewhere [21] the practical and theoretical value of this combined investigation of the artificial scotoma and the angioscotoma, which marks an improvement in the original technique of angioscotometry; I wish only to point out that these findings open the way to an interpretation of the changes observed in angioscotomas quite different from the classic one of Evans and show that the checking of retinal sensitivity should be performed by adding to classic angioscotometry the "slit" examination. This permits a more exact differentiation of angioscotomata (strictly bound to vascular changes) and neuroscotomata (connected with decreased sensitivity of the retina).

The inhalation of oxygen may also act on the lowered visual acuity if a central scotoma which becomes reduced under oxygen inhalation is present, and on the resolving power of the retina, as well as on the light sense, if these functions are impaired by compression of the eyeball. With regard to the ocular motility, I noted that oxygen inhalation enhanced fusional amplitudes and that it also reduced fatigue of convergence and accommodation. In some cases of latent nystagmus the inhalations of oxygen diminished the intensity of the movements.

These effects of oxygen are transitory, and therefore the main use of oxygen inhalations should be in the diagnostic and prognostic, rather than in the therapeutic, field. Repeated inhalations may, however, result in an increasingly better condition; they can, therefore, be employed to enhance the effects of vasodilators, as well as in the simple form of hyperventilation. On account of its action on suppression phenomena in squint, oxygen inhalation is particularly recommended during orthoptic training. To prolong the effects of the increased supply of oxygen, we also employed subcutaneous injections of oxygen (300 to 500 cc.), as well subconjunctival injections 3 to 5 cc.; the effects were less marked than with oxygen inhalation, but lasted longer. It is questionable, however, whether the improvement obtained was connected directly with an increased oxygenation; more probably, it was due to vascular phenomena, since injections of carbon dioxide were followed by the same results.

Subconjunctival injections of oxygen are reported to enhance the resorption of intraocular hemorrhages [35] and lower slightly the intraocular pressure (Bietti [21]). I leave open the problem of the effectiveness of oxygen in retrolental fibroplasia.

With regard to the diagnostic and prognostic use of oxygen, in a disease of the fundus or of the optic pathways the finding that a rise in the oxygen supply reduces the existing scotomata or improves the visual acuity might indicate that the condition is not so severe as it appears, and that at least some area of the fundus may reasonably be expected sooner or later to recover. In glaucoma such a result allows one to foresee improvement, or at least a stabilization, of the ocular functions after the pressure has been lowered by surgical intervention. As has been shown, local or general anoxia, when properly employed, permits the localization of central or peripheral lesions of the optic pathways. In the same way, local or general oxy-

35. Polte, F.: Subkonjunktivale Lufteinspritzung als neue Behandlung bei Augenhintergrundsblutungen, Klin. Monatsbl. Augenh. 117, **2**:186, 1950. Sharkovski, I.: Oxygen Therapy in Ophthalmology, Sovet. med. **2**:29, 1950.

genation may help in the topographic diagnosis. Local oxygenation may be obtained through injection of oxygen into the subconjunctival tissue or into Tenon's capsule, as well as by retrobulbar injection of strong vasodilating drugs, such as nicotinic acid. It has thus been demonstrated that the scotomata of strabismus with amblyopia can be greatly reduced, and may even be made completely to disappear, by an increased local or general oxygen supply, as obtained by the methods described in this paper. This is a reciprocal proof that the inhibition phenomena of strabismus may reach the retina.

Lesions in the peripheral tract of the optic pathways would be improved by both local and general oxygenation, whereas lesions at a higher level would be improved only by general hyperoxia. Even here one must consider the decrease in the retinal "inertia" in the healthy retina produced by oxygen, a decrease which may account for an improvement of as much as 2 degrees in the visual field. Therefore only an improvement beyond this limit, or the disappearance of small scotomata within the limits of the visual field should be taken into consideration for purposes of localization.

Oxygen may help in the diagnosis of aspects of strabismus by showing whether or not it is possible to increase small degrees of fusion in adduction up to a security limit. Such fusion would indicate that there is real fusion, and not simple superposition.[21] Finally, the inhibition of latent nystagmus by oxygen inhalation may be used for the checking of visual acuity, since the nystagmus movements would give a value for the visual acuity below the real value when one eye is occluded.

This presentation of facts has been deliberately brief, and I do not pretend that all the possible aspects of the problem have been exhausted.[36] But, even if this will be the subject for further investigation, I hope to have succeeded in calling the attention of both ophthalmologists and students of aviation medicine to the practical possibilities which the clinical use of anoxia and hyperoxia offers in several fields of ophthalmology.

SUMMARY

After a review of the effects of oxygen deficiency on the visual functions of the normal eye, the results of personal investigations performed by reducing the oxygen supply to the visual apparatus in several morbid conditions of the eye are reported.

A reduced oxygen supply to the visual apparatus can be obtained by producing a general, more or less severe, anoxia (by having the subject breathe an oxygen-poor mixture or by placing him in a depression chamber), and also, if only changes in the oxygen supply to the retina and the optic nerve are required, by exerting with a dynamometer a graded amount of compression, proportional to the arterial pressure of the retina, on the eyeball.

With such a technique, which produces only moderate changes of the visual functions in normal subjects, some visual deficiencies, either signs of an initial or of an apparently cured lesion, may be discovered: enlargement of the blind spot in early glaucoma; appearance of a central scotoma and marked decrease of visual acuity; reduction in the limits of the visual fields in certain neuroretinal diseases; occurrence of ignored hemianopsia in disorders of the intracranial optic pathways;

36. For example, the comparison of the oxygen level in the eye according to the amount of compression and the severity of anoxia.

severe impairment of seemingly normal muscle balance; impairment of the audiometric response, which appears to be typical for certain ocular diseases, e. g., glaucoma, and abnormal decrease of the flicker fusion frequency.

Since the compression of the eyeball reduces the oxygen supply locally, while general anoxia involves the function of whole visual pathways, a difference in results of the two procedures allows sometimes a localization of the lesion.

On the other hand, an increase of the oxygen supply, mainly by inhalation of oxygen at atmospheric pressure, produces a reduction, or even disappearance, of scotomatous areas of the visual field, as well as improvement in the impaired visual functions, generally speaking, in many ocular disorders, thus revealing the presence of areas which have not completely lost their function and are therefore likely to regain a part of it. The therapeutic value of oxygen administration in ophthalmology is discussed.

It may be concluded that the investigation of the behavior of some visual functions under modified oxygen supply in several ophthalmic diseases represents a new procedure which may be of value in ophthalmology.

VASCULAR LOOPS IN THE VITREOUS

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WASHINGTON, D. C.

A PRERETINAL vascular loop, or vascular loop in the vitreous, occurring in an otherwise normal fundus and participating in the blood supply of that fundus is a congenital vascular anomaly that is uncommon and distinct from remnants of the hyaloid artery. The terms prepapillary or preretinal artery (or vein) and vascular or spiral loops in the vitreous have been used interchangeably in the literature to describe this condition.

Such loops in the vitreous are most commonly arterial and unilateral, although they may be venous and, more rarely, bilateral. They arise from one of the main branches of the central retinal vessel.

These vascular loops may have various shapes, sizes, and forms; they may project a short way into the vitreous or very far. These loops are frequently accompanied by a thin glistening veil of connective tissue, which has variously been described as (*a*) remnants of the supportive tissue of the hyaloid artery; (*b*) the posterior hyaloid membrane or (*c*) a clearly seen vessel wall.

The loop may cast a visible shadow on the retina, depending on how oblique is its axis, on its length, etc. These vascular anomalies usually do not interfere with vision, although they may do so if the loop is large enough to fall into the visual axis. It has been pointed out [1] that there is often an associated anomaly, such as astigmatism, hypermetropia, or myopia.

There is often spontaneous pulsation of the loop. Frequently, if none is present, increasing the intraocular pressure by means of pressure on the globe will cause pulsations to appear. These pulsations are synchronous with the carotid pulse.

The first case of a vascular loop in the vitreous was described in 1871 by Liebreich,[2] who no doubt mistakenly thought he saw a persistent hyaloid artery from the disk connect with a "persistent hyaloid vein." This is impossible, of course, since there is no hyaloid vein; the flow from the capillary region of the hyaloid artery is not a back flow but, rather, a forward flow into the veins of the iris.[3]

While Little,[4] in 1881, suggested that the artery he observed might be simply an errant vessel, he reported it as a persistent hyaloid artery. It was not until 1885

From the Department of Ophthalmology, Gallinger Municipal Hospital.

1. Whalman, H. F.: Preretinal Artery, Arch. Ophth. **14**:481, 1935.

2. Liebreich, R.: Demonstration of Diseases of the Eye: Persistent Hyaloid Artery and Vein, Tr. Path. Soc. London **22**:222, 1871.

3. (*a*) Hirschberg, J.: Ein Fall von präpapillarer Gefässschlinge der Netzhautschlagader, Zentralbl. prakt. Augenh. **9**:205, 1885. (*b*) Moll, A.: Glaskörperarterie: Pupillamembran, ibid. **20**:75, 1896. (*c*) Mann, I.: The Development of the Human Eye, Ed. 2, New York, Grune & Stratton, Inc., 1950.

4. Little, W. S.: A Case of Persistent Hyaloid Artery, Tr. Am. Ophth. Soc. **3**:211, 1881.

that Hirschberg [3a] stated definitely that these vascular loops in the vitreous were not part of the embryonal circulation. This assertion was further upheld by the exhaustive studies of Schultze, cited by Kipp,[5] according to whom the embryonal vessels connected with the hyaloid artery disappear entirely and are never transformed into retinal vessels and the new formation of retinal vessels proceeds from the papilla.

This view was upheld by Frost [3b] and by Leber,[6] who, in his review of the subject, supported the conclusions of von Hippel, Günsburg, and Kipp. It is undoubtedly the correct view.

The only histological study was made by Goldstein and Wexler [7] in 1929, when they showed by serial sections that their preretinal artery was connected at its point of origin and termination with branches of the central retinal artery.

The loops have been classified in various ways [6]: (*a*) simple loop with both limbs on disk; (*b*) spiral formation with both limbs on disk; (*c*) arcade formation with both limbs on disk; (*d*) any of these formations with origin on disk and termination in retina. A case in which the loops had origin and termination in the retina has never been described.

Because of the appearance of several cases of these loops in the clinic, I made an extensive review of the literature and found only 54 papers, with 58 case reports.[8] The total number of eyes reported which contained the anomaly was 63.

5. Kipp, C. J.: Two Cases of Anomalies of the Vascular System of the Optic Papilla, Arch. Ophth. **34**:256, 1905.

6. Leber, T., in von Graefe, A., and Saemisch, E. T.: Handbuch der gesamten Augenheilkunde, Ed. 2, Leipzig, W. Engelmann, 1915, Vol. 7, p. 78.

7. Goldstein, I., and Wexler, D.: The Preretinal Artery: An Anatomic Study, Arch. Ophth. **1**:324, 1929.

8. (*a*) Liebreich.[2] (*b*) Kipp, C. J.: Ein Fall von persistierender A. hyaloidea in beiden Augen, Arch. Augenh. **3**:190, 1873. (*c*) Galezowski, J.: Persistance congénitale des vaiseaux hyaloïdiens, Rec. opht. **1**:350, 1874. (*d*) Schapringer, A.: Ein Fall von persistierender A. hyaloidea, Arch. Augenh. **3**:146, 1874. (*e*) Becker, O.: Krankheiten des Glaskörpers, Jahresb. Leistung. Fortschr. Geb. Ophth., p. 500, 1874. (*f*) Riebau, J.: Arteria hyaloidea persistens, Charité-Ann. **1**:648, 1876. (*g*) Little.[4] (*h*) Griffith, A. H.: Persistent Hyaloid Arteries in Each Eye, Ophth. Rev. **1**:246, 1882. (*i*) Czermak, W.: Ein Fall einer in den Glaskörper vordringenden arteriellen Gefässschlinge und Sehnervenausbreitung, Zentralbl. prakt. Augenh. **7**:292, 1883. (*j*) Hirschberg, J.: Über die Angeborene—Ein Fall von Persistenz der tötalen Glaskörper-Gefässe, ibid. **7**:325, 1883. (*k*) Szili, A.: Merkwürdige Schlinge der Netzhautschlagader, ibid. **9**:230, 1885. (*l*) Hirschberg.[3a] (*m*) Frost, W. A.: Abnormal Course of a Branch of the Arteria Centralis Retinæ, Tr. Ophth. Soc. U. Kingdom **7**:171, 1887. (*n*) Bock, E.: Erfahrungen auf dem Gebiete der Augenheilkunde, Wien, J. Šafář, 1891, p. 60. (*o*) Michel, J.: Lehrbuch der Augenheilkunde, Ed. 2, 1890, p. 360. (*p*) Wachtler, G.: Ein Fall von beiderseitiger in der Glaskörper vordringender Arterienschlinge, Wien. med. Wchnschr. **10**:340, 1896. (*q*) Moll.[3b] (*r*) Günsburg, F.: Ein Fall von in den Glaskörper vordringender Arterienschlinge, Klin. Monatsbl. Augenh. **37**:173, 1899. (*s*) Bondi, H.: Zwei Fälle einer den Glaskörper vordringender Arterienschlinge, ibid. **37**:339, 1899. (*t*) Hirsch, C.: Ein Fall von in den Glaskörper vordringender Gefässschlinge der Netzhautschlagader, ibid. **37**:341, 1899. (*u*) Wintersteiner, H.: Bericht über die deutsche ophthalmologische Litteratur: II. Semestre 1899, Ztschr. Augenh. **4**:611, 1900. (*v*) Bär, C.: Ein Fall von in den Glaskörper vordringender Arterienschlinge in einem durch Embolie der Zentralarterie erblindeten Auge, Klin. Monatsbl. Augenh. **39**:307, 1901. (*w*) Fehr, R.: Eine Gefässanomalie auf der Sehnervenscheibe, Zentralbl. prakt. Augenh. **26**:234, 1902. (*x*) Alexander, L.: Ein weiterer Fall von in den Glaskörper vordringender Arterienschlinge, Ztschr. Augenh. **10**:188, 1903. (*y*) van Geuns, J. R.: Ein Fall von in den Glaskörper vordringender Arterienschlinge, ibid. **11**:316, 1904. (*z*) Felix, H.: Een

(Footnote continued on next page)

Three references by Aust[8k'] cannot be corroborated and are considered spurious. The case by Scarlett[9] appears to be one of postinflammatory and/or posthemorrhagic origin and is not included here. In one case[10] a moving loop was contained in a congenital cyst, but since the loop was beneath instead of in front of the retinal vessels, it is not included in the total cited above.

Of this number, there are 11 cases of venous loops.[11] There were only five cases of bilateral occurrence of the vascular loops.[12]

Three authors reported more than one case.[13] Apparently, only three cases of an arterial loop with a concomitant venous loop in the same eye[14] have been reported. Two cases of embolism in eyes containing these vascular loops[8x,c'] have been reported.

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vaatlis in het glasvocht, Geneesk tijdschr. Nederl.-Indië **44**:319, 1904. (*a'*) Kipp.[5] (*b'*) Crampton, G. S.: Retinal Vessels Extending Forward in Vitreous, Tr. & Stud. Coll. Physicians Philadelphia **37**:424, 1915. (*c'*) Walker, C. H.: Thrombosis of the Inferior Temporal Branch of the Arteria Centralis in an Eye with a Persistent Hyaloid Artery and Vein Caused by Exposure to Direct Sunlight, Tr. Ophth. Soc. U. Kingdom **23**:279, 1902. (*d'*) Segal, L. M.: Congenital Abnormal Arteries in the Vitreous Body, Vestnik oftal. **23**:357, 1906. (*e'*) Worton, R.: A Case of Congenital Arterial Loop Projecting into the Vitreous, Ophth. Rev. **29**:191, 1910. (*f'*) Nomura, S.: Vessels in Vitreous, Nippon Gankwa Gakukwai Zasshi, 1913; abstracted, Ophth. Year-Book **11**:251, 1914. (*g'*) Márquez, M.: Tronco arterioso penetrante nel vitreo, di fronte al disco ottico, Arch. oftal. hispano-am. **14**:25, 1914. (*h'*) Rönne, H.: Venenschlinge auf der Papille, Klin. Monatsbl. Augenh. **56**:570, 1916. (*i'*) Francis, L. M.: Anomalous Spiral Looping of Retinal Artery, Am. J. Ophth. **4**:202, 1921. (*j'*) Musy, E.: Trois cas d'anomalies congénitales de l'oeil, Rev. gén. opht. **34**:467, 1920. (*k'*) Aust, O.: Ein Fall in den Glaskörper verdringender Arterienschlinge und Versuch der Erklärung dieser Anomalien, Ztschr. Augenh. **51**:45, 1923. (*l'*) Merrill, U. H., and Wagener, H. P.: Anomalous Spiral Looping of a Retinal Vein, Am. J. Ophth. **7**:177, 1924. (*m'*) Hoeg, N.: Über prominente arterielle Gefässschlinge auf der Papille und die Windungsrichtung, bei der Drekung von Retinalgefassen, Verhandl. Ophth. Gesellsch., 1925. (*n'*) Coats, G.: Peculiar Appearance of a Retinal Vein, Ophth. Rev. **24**:27, 1905. (*o'*) Menacho, M.: Gefässanomalien des Augenhintergrundes, Arch. oftal. hispano-am. **26**:253, 1926. (*p'*) Yudkin, A. M.: Bilateral Prepapillary Vascular Loops of the Retinal Artery, Arch. Ophth. **56**:474, 1927. (*q'*) Goldstein and Wexler.[7] (*r'*) Hartmann-Sourdille: Anomalie vasculaire de la retine chez une malade opérée d'un tumeur cérébrale, Bull. Soc. opht. Paris **4**:187, 1930. (*s'*) Fischer, F.: Beitrag zu den Fehlbildungen des Auges (Netzhautarterienschlinge-Linsenektopie), Ztschr. Augenh. **70**:158, 1932. (*t'*) Androgne-Pereira: Su di un raro aspeto del fondo oculare, Arch. oftal. Buenos Aires **7**:335, 1932. (*u'*) Tillé, H.: Anses vasculaires artérielles et veineuses pénétrant dans le corps vitré ou reliquats d'artére hyaloide: Colobomes bilatéraux de l'iris, Bull. Soc. opht. Paris **6**:452, 1933. (*v'*) Dalsgaard-Nielsen, E.: On Arterial Loops in the Vitreous, Acta ophth. **12**:385, 1934. (*w'*) Whalman.[1] (*x'*) Yagamata, S., and Fukushima, S.: Einige Fälle von angeborener Netzhautgefassanomalie, Chuo. Gank-Iho. **28**:25, 1936. (*y'*) di Marzio, Q.: Fundus oculi: Diagnostica oftalmoscopica, Rome, L. Salomone, 1937. (*z'*) Mózzetti, M.: Sulle anomalie dei vasi retinicie in particolare modo sull'aneurisma cirsoide della retina, Boll. ocul. **17**:455, 1939. (*a''*) Shimizu, M.: A Case of Congenital Vascular Anomaly of the Retina, Acta Soc. Ophth. Japan **45**:572, 1941. (*b''*) Oxilia, E.: Anomalie vascolari della retina: Ansa arteriosa prepapillare, Ann. ottal. e clin. ocul. **72**:408, 1946.

9. Scarlett, H. W.: New Vessel Formation in the Vitreous, Am. J. Ophth. **9**:521, 1926.

10. Levitt, J., and Lloyd, R. I.: Congenital Prepapillary Cyst Containing a Moving Vascular Loop, Am. J. Ophth. **22**:760, 1939.

11. Fehr,[8w] Crampton,[8b'] Walker,[8c'] Nomura,[8f'] Rönne,[8h'] Merrill,[8l'] Coats,[8n'] Tillé,[8u'] Yagamata and Fukushima,[8x'] Mózzetti,[8z'] Shimizu.[8a'']

12. Griffith,[8b] Wachtler,[8p] Yudkin,[8p'] Tillé,[8u'] Whalman.[1]

13. Gunsburg,[8r] Crampton,[8b'] Dalsgaard-Nielsen,[8v']

14. Fehr,[8w] Nomura,[8f'] Tillé.[8u']

Having been exceptionally fortunate in seeing several cases, I report two cases of bilateral preretinal arteries, two cases of unilateral arterial loop, one case of unilateral venous loop, and one case of a loop that did not project into the vitreous, but remained confined to the plane of the papilla, similar to Szili's case.[8k]

REPORT OF CASES

CASE 1.—M. M., a 14-year-old Negro girl, came to the clinic because in a routine check-up at the school eye clinic she had been found to have visual acuity of 20/30 — 2 in the right eye and 20/25 — 2 in the left eye.

Right Eye.—On the nasal aspect of the disk there was an artery (Fig. 1) extending approximately 10 D. into the vitreous (Fig. 2). This artery appeared to have its origin in the inferior branch of the central retinal artery. The outgoing branch twisted clockwise for 180 degrees, when it then curved forward, forming a strip of vessel parallel with the iris-lens diaphragm. The vessel then bent posteriorly, crossed the efferent limb and turned inferiorly, where it reached the disk margin. It then ran clockwise along the disk margin from 3:30 to 7 o'clock, curving under and over a large vein in the process. It left the disk at approximately 7:30 o'clock, where it was distributed as a relatively large inferotemporal artery. Several small arterial twigs were given off in its course along the disk margin. There was a cilioretinal artery from the temporal side of the disk. The over-all twist of the artery was counterclockwise, i. e., to the patient's right. A definite strong pulsation was seen in the most forward portion of the loop. Owing to its length, no clear-cut shadow was cast on the retina. There was no glistening tissue accompanying the loop.

Left Eye.—A small nubbin of vascular tissue appeared to be part of the inferior nasal branch of the central retinal artery (Fig. 3). It was covered by a fine veil of glistening connective tissue. It had the appearance of a tight knot of tissue and was raised approximately 2 D. above the retinal plane. Springing from this knot were two small arteries, which passed to the superior nasal and inferior nasal quadrants. The inferior temporal artery ran directly laterally toward the disk margin and then made a sharp curve, still on the disk, of 180 degrees. It was distributed to the inferior temporal and a part of the inferior nasal quadrant. A very fine pulsation of the loop could be seen. Owing to its form and position, no shadow was cast on the retina.

The superior temporal artery was not remarkable, and the superior temporal branch of the central retinal vein paralleled it. Two cilioretinal arteries left the disk at 2:30 and 3 o'clock.

Refraction.—With 5% homatropine hydrobromide cycloplegia, the correction was + 0.50 D., axis ∞ 90 for each eye, resulting in 20/20 — 1 vision in each eye.

CASE 2.—Y. S., a 17-year-old Negro school girl, was referred from school because in the routine check-up she had been found to have poor vision in the right eye. The patient had been aware of this poor vision, but it had not interfered with her schoolwork in any way.

Examination revealed 20/200 vision in the right eye and 20/20 in the left eye.

Right Eye.—The superior branch of the central retinal artery was distributed in normal fashion. There were three divisions of the inferior branch of the artery. The most remarkable finding, however, was the inferior branch of the central retinal vein (Fig. 4*A*). This vessel originated from the upper half of the disk, crossed the disk, and passed inferiorly. It then protruded into the vitreous approximately 3 D., where it became wrapped around itself in a corkscrew fashion (Fig. 4*B*). The apex was covered with fine glistening tissue, but it was possible to discern the underlying curves. Upon its reapproaching the disk, it was divided into branches which drained the inferior half of the retina.

Left Eye.—This eye was essentially normal.

Refraction.—With 5% homatropine hydrobromide cycloplegia, hypermetropia of + 2.50 D. was revealed. With this correction, vision was improved to 20/40 — 2 in the right eye.

CASE 3.—B. J., a 6-year-old Negro girl, was seen in the emergency room, with the history of having been hit two days previously with a rock. A small corneal denudation was noted. Atropine ointment was instilled, and the eye was patched. Upon her return to the clinic the following day, vision was found to be 20/20 in each eye, but the right fundus showed a preretinal arterial loop (Fig. 5).

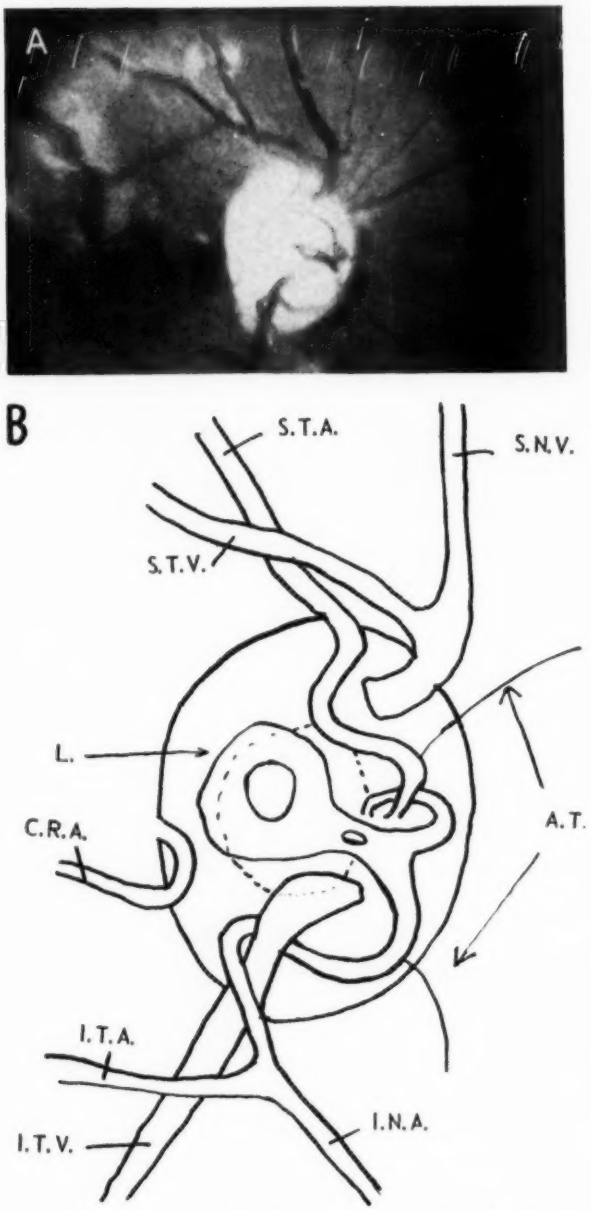

Fig. 1 (Case 1; right eye).—*A*, origin of preretinal artery from inferior branch of central retinal artery. The loop itself is out of focus and can only vaguely be discerned, in the middle of the disk.

B, diagram of *A*. Several nasal arterial twigs (*A.T.*) are given off. There is a cilioretinal artery at 9 o'clock.

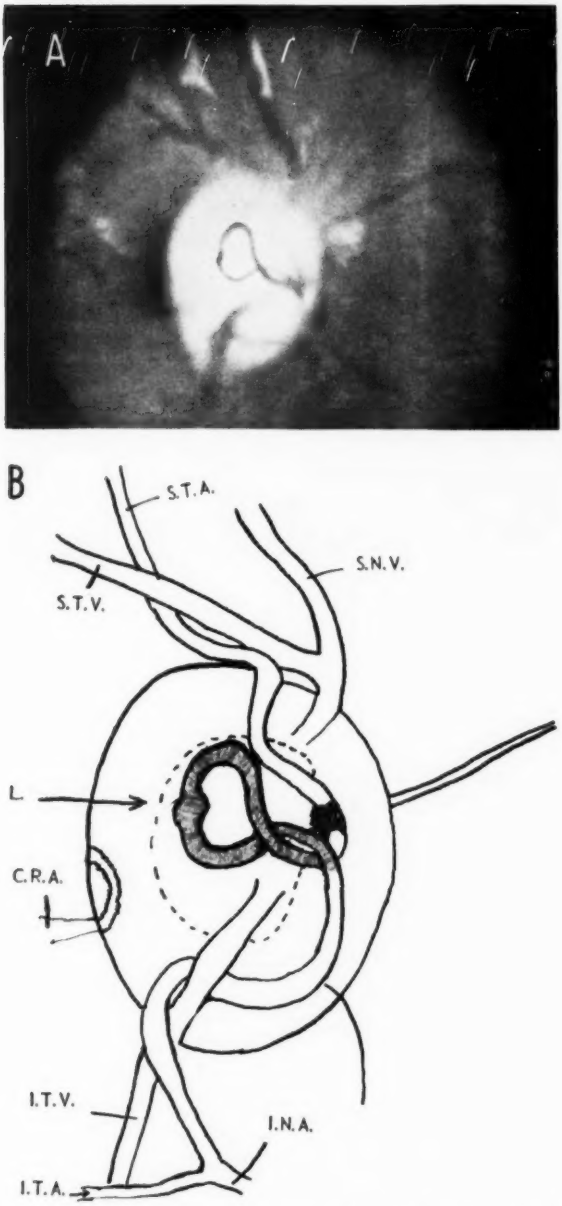

Fig. 2 (Case 1; right eye).—*A*, loop in focus, with disk blurred in background. Strong pulsations could be seen in the forward-passing portion of the loop.

B, diagram of *A*. The loop (*L*) is clearly outlined. The counterclockwise twisting is shown. The disk proper, as well as vessels in the plane of the disk, is poorly outlined.

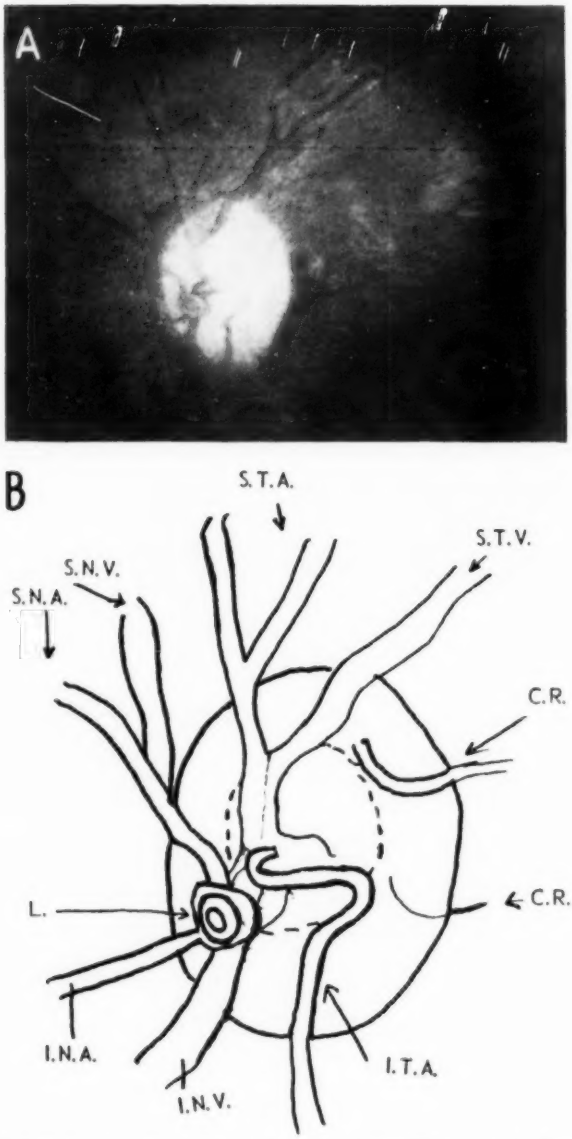

Fig. 3 (Case 1; left eye).—*A*, small, tight arterial "knot" seen projecting from disk at approximately 8 o'clock. Whitish, glistening tissue can be seen interwoven in the "knot."

B, diagram of *A*. Note the small, tightly twisted loop in the inferior nasal portion of the disk. The superior and inferior nasal arteries (*S.N.A.*; *I.N.A.*) arise in this loop (*L*). Note the curving course of the inferior temporal artery (*I.T.A.*).

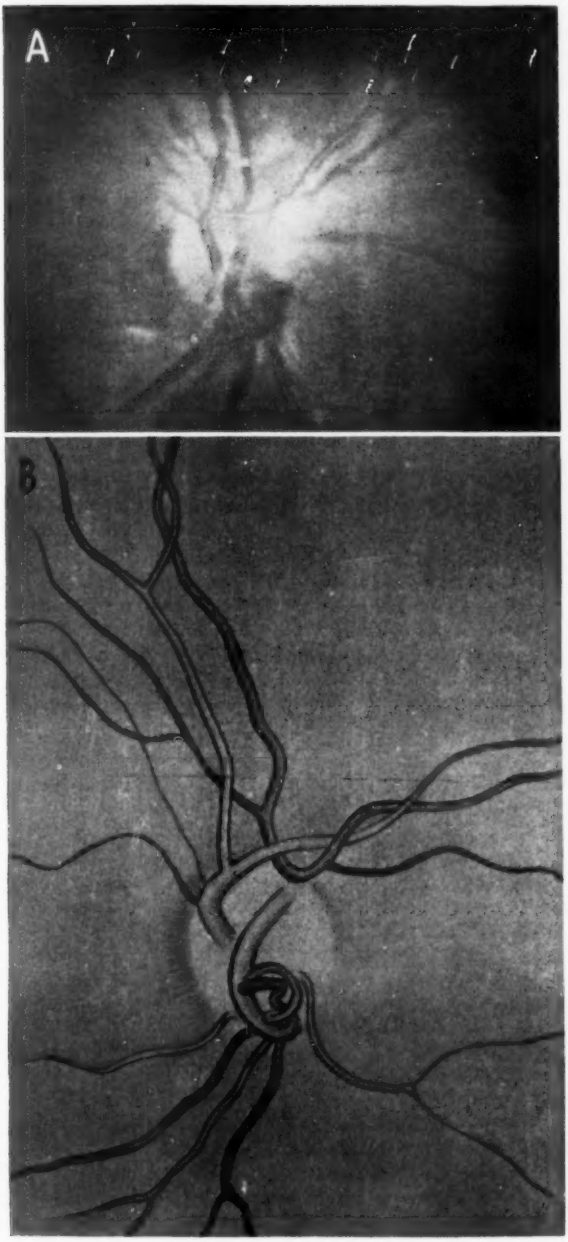

Fig. 4 (Case 2; right eye).—*A*, inferior branch of central retinal vein. It is wrapped around itself in corkscrew fashion.

B, drawing of *A*, showing the counterclockwise twisting of the vein.

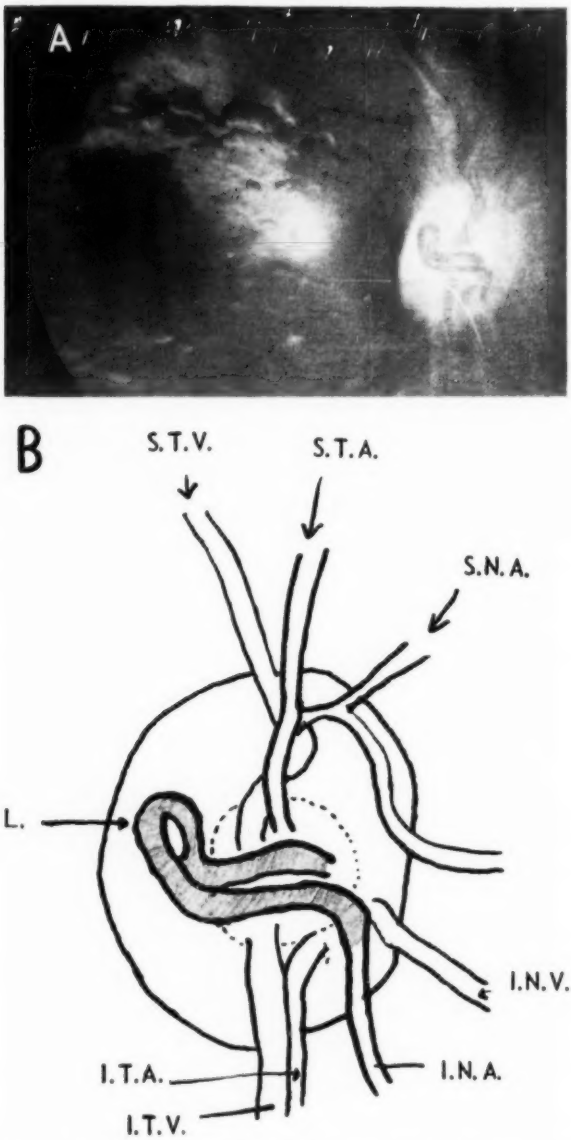

Fig. 5 (Case 3; right eye).—*A*, inferior nasal artery projecting into vitreous directly in front of disk.

B, inferior nasal artery forming laterally lying loop (*L*.).

Right Eye.—The inferior branch of the central retinal artery appeared to divide into two branches. The nasal of the these branches passed forward into the vitreous for approximately 3 D., then temporally and horizontally and forward again, where it made a 180-degree turn and followed itself back to the disk margin. It was distributed to the inferior nasal quadrant. It showed a pulsation synchronous with the radial pulse. No shadow was cast on the retina. There was a small amount of connective tissue at the base of the loop. The inferior temporal artery was not remarkable in its distribution. The superior temporal artery gave off a branch at 12 o'clock at the disk margin; this branch followed the disk margin clockwise to 3 o'clock, where it passed directly nasally, thus supplying a part of the inferior nasal quadrant.

Left Eye.—Except for filmy connective tissue in the middle of the left disk, the eye was entirely normal.

CASE 4.—J. R., a 34-year-old Negro restaurant worker, entered the hospital emergency room because of recurrent epistaxis. In examining the patient, it was discovered that his blood pressure was 200/110. The fundi were then examined, and the following findings were noted:

Right Eye.—Coming from the center of the disk and running nasally toward the disk margin at 3:30 o'clock was a small artery, which at the margin of the disk suddenly turned and ran forward into the vitreous for approximately 1 D. (Fig. 6). It then made a 180-degree turn and returned to the retina at 3:30 o'clock. From there it followed the disk margin, crossing the large inferior branch of the central retinal vein, to 7:00 o'clock, where it ran onto the retina in the inferior temporal quadrant. There were three cilioretinal arteries in this eye. A large branch of the central retinal vein also passed nasally and drained most of the superior and inferior nasal quadrants.

Left Eye (Fig. 7).—Coming exactly from the center of the disk, an arterial loop protruded into the vitreous. This artery passed nasally approximately one-fourth of the disk and then ran superiorly into the vitreous. Turning counterclockwise, it formed a figure-of-eight, which lay vertically and oblique to the anteroposterior axis. The artery then passed to the edge of the disk at 9 o'clock and ran around the margin of the disk counterclockwise for 90 degrees, crossing the large inferior branch of the central retinal vein in the process. On the retina, it was distributed as the inferior temporal artery. The loop itself was seen to pulsate and cast a shadow on the underlying retina and superior temporal branch of the central retinal vein. There was no suggestion of any accompanying glial tissue.

CASE 5.—L. H., a premature Negro girl, weighing 3 lb. ½ oz. (1,322 gm.), was observed at 2 weeks of age, during a routine examination for the early changes of retrolental fibroplasia. She was found to have a preretinal artery at that time. At the age of 2 months 21 days the condition was as follows:

Right Eye.—Coming from the center of the disk was an artery which was apparently the inferior branch of the central retinal artery, but instead of curving inferiorly at the disk margin, the artery extended directly toward the lens for approximately 7 to 8 D. It then turned upon itself and passed superiorly to the outgoing vessel, thus forming a small loop. It then passed nasally to the outgoing vessel, and thus was twisted counterclockwise, or to the patient's right. It passed back to the plane of the disk, where, at 5:30 o'clock, it divided into two small arteries, the nasal one supplying the inferior nasal quadrant and the other supplying the inferior temporal quadrant. Through this bifurcation a large vein passed. These inferior vessels appeared smaller than the superior vessels. There was a small amount of glistening material along the entire extent of the vascular loop. The disk appeared somewhat oval. The left eye appeared essentially normal. Photographs of the fundus were impossible to obtain because of the age of the patient.

CASE 6.—C. W., a 10-year-old Negro girl, was sent in for a routine examination of the eyes. Vision was 20/20 in each eye. In the left eye, however, there was an interesting arterial loop on the disk (Fig. 8). The inferior branch of the central retinal artery emerged from the center of the disk and proceeded directly inferiorly. Approximately halfway to the disk margin, however, the artery made a 360-degree turn, thus forming a circle and coming to lie on itself. It then proceeded to the disk margin at 6 o'clock. Running out a short distance onto the retina, it divided into a nasal and a temporal branch, which were distributed in their respective areas in the inferior half of the retina.

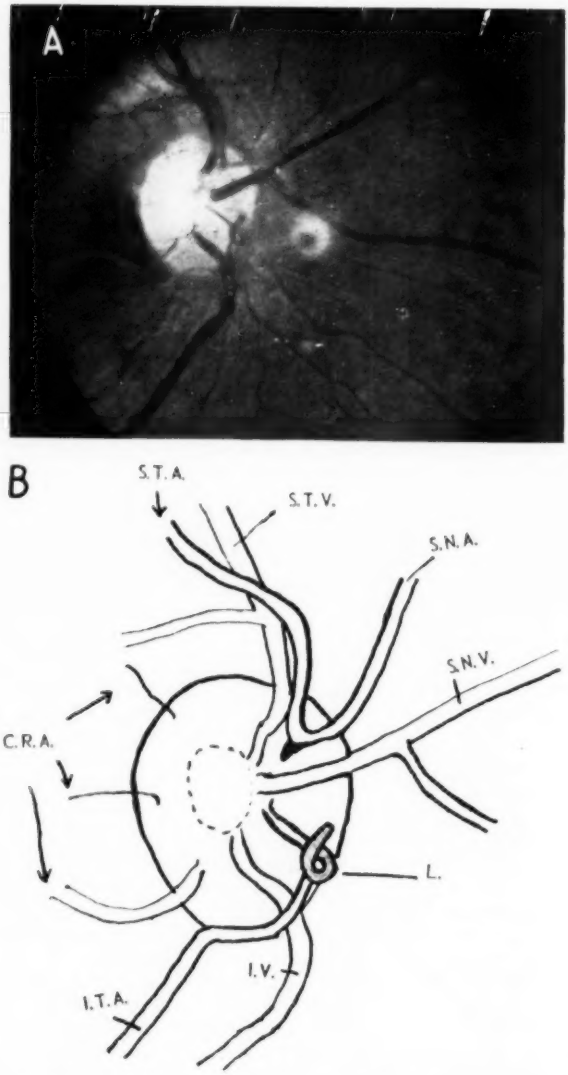

Fig. 6 (Case 4; right eye).—*A*, small arterial loop projecting into vitreous in front of disk at approximately 4 o'clock. The artery finally passes onto the retina at 7 o'clock.

B, diagram of *A*. Note the three cilioretinal arteries (*C.R.A.*) on the temporal side of the disk.

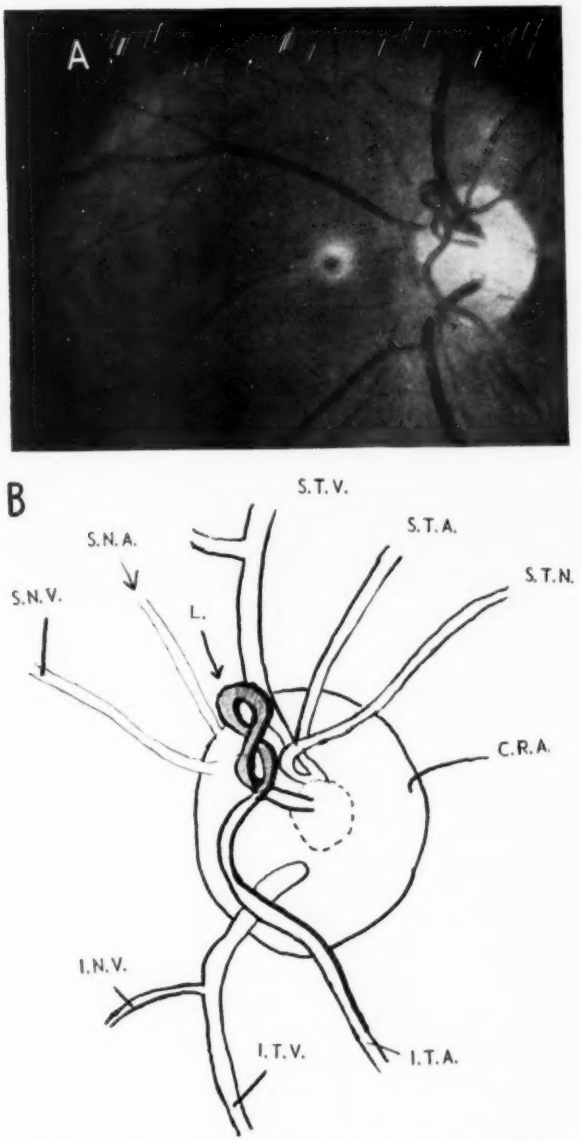

Fig. 7 (Case 4; left eye).—*A*, figure-of-eight knot formed by inferior branch of central retinal artery at upper nasal quadrant of disk. The loop lies in a sufficiently oblique position to overlie the margin of this area. It casts a shadow on the underlying retina.

B, diagram of *A*. There is a small cilioretinal artery at the temporal side of the disk.

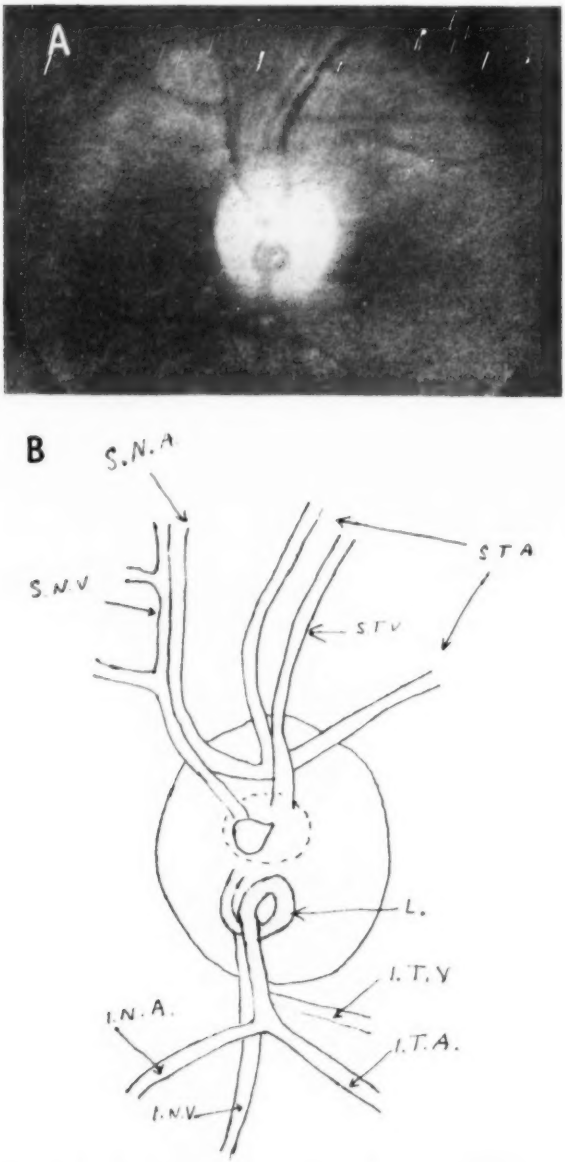

Fig. 8 (Case 6; right eye).—*A*, the 360-degree arterial circle lying on the disk at 6 o'clock. This was not elevated above the plane of the retina.

B, diagram of *A*. Note how the artery divides into temporal and nasal branches after the 360-degree circle has been completed.

While not a true vascular loop in the vitreous, this 360-degree circle probably represented the same process as the others. It was similar to another case reported [8k] and is included because of its obvious interest in this connection.

COMMENT

The infrequence of the occurrence of these vascular loops is shown by the literature. I have been fortunate in collecting the number of cases presented.

Various theories have been advanced concerning the origin of these loops and etiologic factors in their formation. It is now an accepted fact that they do not represent remnants of the old hyaloid artery itself. This fact has been pointed out by Hirschberg,[3a] von Hippel,[6] Günsburg,[8r] Mann [3c] and others. The original of congenital tortuosities can be explained only as the result of considerably increased longitudinal growth of one of the new retinal vessels during the period of development. The exact cause of this growth has not definitely been shown.

However, it is known that at the fourth month of fetal life a small bulbous swelling appears from the glial tissue covering the hyaloid artery where it passes through the disk. This bulbous swelling enlarges with time and gives rise to two sprouts (buds), one superior and the other inferior, these being the beginnings of the superior and inferior branches of the central retinal artery. Other arterial twigs arise from these buds and from the central mass of cells. Capillaries then grow out and ramify peripherally in the nerve fiber layer of the retina, until they reach the ora serrata at the fetal age of 8 months, at which time their development is complete.

At some time, then, about the fourth or fifth month, something goes awry in these vascular loops in the vitreous, so that newly forming arteries in this area of the disk are pushed forward. This abnormality has been suggested by various authors [15] as due to the additional stress and strain to which the new-forming small retinal arteries, taking a right-angle bend at the disk margin, are subjected at this point. In a few cases, owing to a factor as yet unknown, this stress and strain produce an elongation of the vessel at this point in the anteroposterior axis, thus causing the artery to lie in front of the retina. Eddies in the stream at the sharp curve may result in torsion of the loop as it forms. This theory is supported by the fact that in all the cases reported to date the loops have had at least one limb on the disk.

However, in view of the fact that the hyaloid artery maintains its functions past the fifth month, beginning to atrophy only in the seventh month of fetal life, it would be difficult to envisage the development of much pressure at this right-angled bend, where the smaller new-formed vessels are taking their origin. In view of the infrequence of this condition, there must be a mechanism in addition to this right angled turn which causes the retinal artery to push forward into the vitreous.

It is possible, however, that a premature closure or reduction in patency of the hyaloid artery anterior to the disk, due to localized hyperplasia of the cells in the wall of the hyaloid artery, or to vasculitis, or some other condition, would increase the intraluminal pressure in these lateral-growing new vessels.

It is conceivable that in this instance the increased intraluminal arterial pressure would heighten the hydrostatic "push" at the anterior part of the right angle of the artery. The continued pounding of the blood at this point would tend to cause

15. Kipp.[5] Leber.[6]

the pliable new vessel to push forward. Possibly, once a vessel had pushed forward slightly, this enlongation, by acting as a shock absorber, would reduce the hydrostatic effect sufficiently so that other vitreous loops would not be formed. This theory is supported by the fact that no case of two arterial loops in the same eye has been reported. A somewhat different explanation would be needed for venous anomalies.

The percentage distributions were calculated by Oxilia [8b''] as follows: inferior branch of central retinal artery, 45%; inferior temporal artery, 25%; superior temporal artery, 20%; superior nasal artery, 8%; superior branch of central retinal artery, 2%. The corresponding figures for venous loops are superior temporal vein, 45%; superior nasal vein, 30%; inferior branch of central retinal vein, 25%; inferior nasal vein, 25%.

Of the eight loops presented in this paper, the distributions were as follows: inferior branch of central retinal artery, 4; inferior temporal artery, 2; inferior nasal artery, 1; inferior branch of central retinal vein, 1.

It has been pointed out that the twist of these loops with more than one 360-degree turn is almost always to the right side,[8m'-b''] i. e., counterclockwise as one looks in at the fundus. Hoeg believed that these vascular loops are entirely mechanical products resulting from an oblique direction of elastic fibers in the vessel wall. Dalsgaard-Nielsen [8v'] emphasized that other congenital anomalies are sometimes present.

The fact that embolism has been observed in two of the reported cases makes it possible that the relatively sharp angles taken by such anomalous vessels are more conducive to embolism than the normal retinal vessels.

As mentioned previously, the vascular loops as described in this paper occur in essentially normal fundi in essentially normal persons. It should be remembered that vascular anomalies and cerebral tumors, especially in connection with arteriovenous aneurysms of the midbrain and facial nevi, have been described.[16] If other neuro-ophthalmological signs are present, this fact should be borne in mind and the possibilities explored.

In the majority of cases in the literature, and in my series, the vascular loops were found in routine examinations of the fundus of patients who were unaware of the condition. One may assume, therefore, that these vascular loops are commoner than the literature indicates, and that they come to the attention of the examining physician only when he sees them in examining the fundus for some other reason.

SUMMARY

Preretinal or prepapillary vascular loops occurring in otherwise normal eyes are congenital phenomena. These loops are patent vessels and carry blood that is distributed to the retina.

A review of the literature revealed 54 papers presenting a total of 58 cases, or 63 eyes with vascular loops in the vitreous. Six more cases with a total of eight eyes, are now presented; two were of bilateral arterial loops, two of unilateral arterial loop, one of venous loop, and one of loop on the disk. Speculations regarding the etiology of these interesting anomalies are presented. The period of intrauterine development involved is, at most, from the fourth to the seventh month.

16. Hartmann and Sourdille.[8r'] Wyburn-Mason, R.: Arteriovenous Aneurysm of Mid-Brain and Retina: Facial Nævi and Mental Changes, Brain **66**:163, 1943.

The vascular loops presented in this paper are entirely separate and distinct from remnants of the hyaloid artery, vascular changes in retrolental fibroplasia, and the neovascularization that occurs after intraocular hemorrhage and/or inflammatory conditions in adult life.

These loops are found in routine examination by the ophthalmologist or in examination of the fundus by the more astute and thorough internist.

The actual incidence of such loops is undoubtedly much greater than the literature indicates.

It should be remembered that similar, but not identical, retinal vessels have been described in patients with arteriovenous aneurysms of the midbrain, as well as after intraocular hemorrhages or inflammatory conditions.

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EVALUATION OF PLASTIC SPECTACLE LENSES

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THE RECENT development of optically clear plastics marks the first basic change in materials used for spectacle lenses since their introduction. Some of the more recent compounds bid well to supersede crown glass.

Beginning with Celluloid, in 1870, the organic plastic industry has crossed many hurdles: (1) optical clarity, (2) water absorption, (3) light stability, (4) thermal expansion, (5) thermoplasticity, (6) shrinkage, and (7) warping. Plastics may be divided into two groups according to their reaction to heat: thermolabile (thermoplastics), or those that soften under heat, and thermosetting, or those which once hardened under heat cannot be softened by it. Methyl methacrylates, such as Plexiglas, Lucite, Perspex, Transpex I, and the Tulca lens (California, 1937-1939), and most contact lenses are thermoplastics with softening points from 122 to 254 F. More complex allyl resins (C. R. 39; allyl diglycol carbonate), as used in present Armorlite lenses, are thermosetting.

Softness has been a serious drawback in all optical plastics, and present plastic lenses still scratch more easily than glass. Other disadvantages, however, are not serious: 1. Thermoplastic (not thermosetting) lenses may be distorted by short blasts of heat, as when an oven door is opened, but generally withstand temperature that the body can endure. 2. Plastics have greater susceptibility than glass to attack by chemicals. 3. The index of refraction (1.49 to 1.51) is slightly less than that of crown glass (1.51 to 1.53), and a small correction factor is required when one is using a Geneva lens measure. 4. The usual edge-grinding machines are not efficient on the softer of these lenses. 5. The lenses are inflammable but are with difficulty ignited with household matches and burn more slowly than cellulose acetate and cellulose acetate butyrate,[1] used in most plastic frames. 6. The cost of plastic lenses is moderately more than that of glass lenses in lower strengths and increases sharply in higher-power prescriptions.

Plastic lenses offer the following real advantages: 1. The impact resistance of some plastics is greater than that of case-hardened glass. 2. Fragmentation, when it does occur, usually yields larger and more obtuse segments than occurs with broken glass. 3. The weight is only 40 to 50% that of glass. 4. Light transmission is 5 to 8% better than that of glass. 5. The tendency to fogging is reduced 60 to

Presented at a meeting of the Louisville Eye and Ear Society, Sept. 11, 1952.

From the University of Louisville School of Medicine and Industrial Research Institute.

1. Van Portfliet, P., and Fralick, F. B.: Inflammability of Plastic Eyeglass Frames, Am. J. Ophth. **34**:1727-1729 (Dec.) 1951.

75% because of the low thermal conductivity. 6. Plastics are less affected than glass by welders' splatter and high-velocity particles.[2] 7. Fewer rings are apparent in strong minus lenses. 8. Production by molding or casting eliminates surfacing procedures.

Hardness, which is a conglomeration of properties that defines with difficulty, remains a pivotal problem. Here, commercial claims and pseudoscientific data become somewhat self-indulgent. Figures of different manufacturers—as is true of various hardness tests themselves—usually cannot be compared. Physicists precisely describe factors participating in hardness, such as scratch resistance, abrasion resistance, impact resistance, cutting resistance, and resiliency, or rebound hardness, but only approximate mathematical correlation exists among these factors.

The basic reference for hardness is the Mohs scale[3] (1822) of 10 minerals arranged in ascending order of hardness. Each mineral will scratch the one below it and not those above it, but subsequent studies have shown that intervals between these minerals are uneven (Fig. 1). For more critical analysis, dozens of empirical tests have been standardized by the American Society for Testing Materials, the American Standards Association, the National Bureau of Standards, and the British Standards Institution. These are variously critical measures of (1) diamond-point

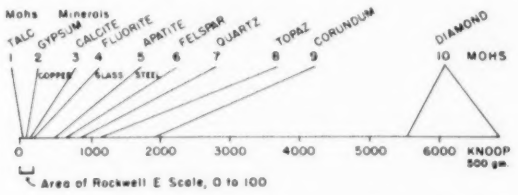

Fig. 1.—Approximate relationship of hardness scales of Mohs, Knoop, and Rockwell E.

scratches, (2) recoil, (3) haze produced by abrasives, (4) indentation under load, and (5) residual indentation after removal of load.[4]

Indentation procedures (Brinell, 1900; Meyer, 1908; Ludwik, 1908; Rockwell, 1919; Vickers, 1925; Knoop, 1939) are the most standard tests. The Rockwell hardness tester[5] makes rounded indentations of 0.2 to 0.002 mm. and has a direct reading dial (Fig. 2). The depth of indentation makes Rockwell machines unsuitable for brittle materials. The Tukon-Knoop[6] microindenter makes sharp, rhomboidal penetrations only 0.5 to 30 μ in depth and is applicable to most materials. Test specimens should be polished and perfectly plane. Indentations are measured

2. Durham, D. G.: Plastic Lenses in Industry, Tr. Am. Acad. Ophth. **53**:680-682 (July-Aug.) 1949.

3. Bernhardt, E. C.: History of Hardness Tests, Bull. Am. Soc. Testing Materials **157**:49-53 (March) 1949.

4. Boor, L.: Indentation Hardness of Plastics, Proc. Am. Soc. Testing Materials **44**:969-991, 1944.

5. Lysaght, V. E.: Indentation Hardness Testing, New York, Reinhold Publishing Corporation, 1949.

6. Knoop, F.; Peters, C. G., and Emerson, W. P.: A Sensitive Pyramidal Diamond Tool for Indentation Measurements, Research Paper 1220 U. S. Department of Commerce, Bureau of Standards, July, 1939.

under a microscope. Because of the sharp-edged, diamond indenter, Knoop figures correlate better with scratch determinations (Martens, Graton, Bierbaum) than do Rockwell figures.

Photoelectric estimation of surface haze produced by air-borne particles or standard abrasive wheels (Tabor,[7] Bernhardt,[8] Boor,[9] Schiefer and associates,[10] and Starkie [11]) do not have widespread application. Results do not correlate with indentation or scratch tests and at times seem to show less haze after than before the abrading procedure.[12]

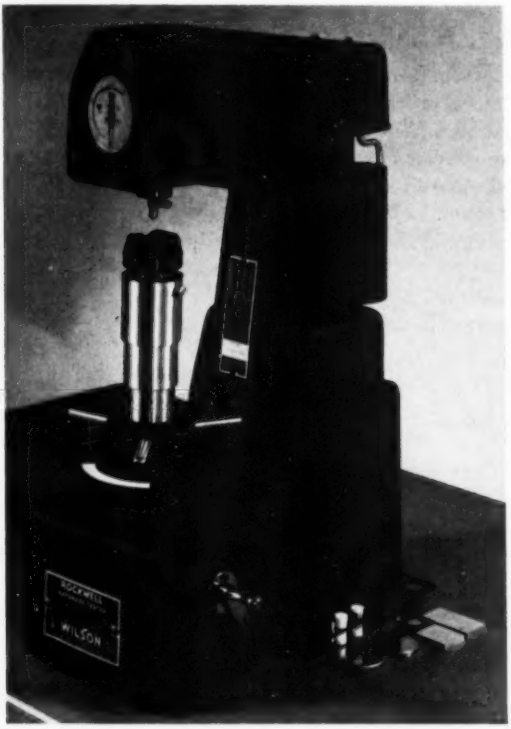

Fig. 2.—Rockwell indentation-hardness testing machine.

7. American Standard Safety Code Z 26.1, 1950, Tests No. 17 and 18, New York, American Standards Association, May, 1950.

8. Bernhardt, E. C.: Scratch Resistance of Plastics, Mod. Plastics **26**:123-126 (Oct.) 1948.

9. Boor, L.: Mar Resistance of Plastics to Abrasive Particles, Mod. Plastics **20**:79 (Sept.) 1942.

10. Schiefer, H. F.; Crean, L. E., and Krasney, J. P.: Improved Single-Unit Schiefer Abrasion Testing Machine, Journal of Research, U. S. Department of Commerce, Bureau of Standards, 1949, Vol. 42, pp. 481-497.

11. Starkie, D.: Hardness and Scratch Resistance of Plastics, J. Soc. Glass Technol. **26**:130-144 (June) 1942.

12. Boor, L.; Ryan, J. D.; Marks, M. E., and Bartoe, W. F.: Hardness and Abrasion Resistance of Plastics, Bull. Am. Soc. Testing Materials **145**:68-73 (March) 1947.

Our purpose has been to evaluate commercial lenses according to the best standard procedure and to compare them with a familiar industrial plastic, Plexiglas (methyl methacrylate). Test blanks were purchased locally in plano strength. Plastic lenses currently available in prescription form are Armorlite, manufactured from allyl diglycol carbonate (supplied by Pittsburgh Plate Glass Company) by the Armorlite Lens Co., Inc., of Pasadena, Calif., and I-gard, manufactured from Transpex I,[13] which is methyl methacrylate coated with allyl methacrylate, by the Combined Optical Industries, Ltd., of Slough, England. A third lens, Plastolite, is available in plano strength only and is manufactured from a base of allyl diglycol carbonate by the American Optical Company, at Brattleboro, Vt.

Because the I-gard lens has been described as surface-coated, all tests were run on the blanks in original form, without lapping or blocking. Curvature of the blanks makes them unsuitable for scratch tests. For hardness we have used the Rockwell [14] macroindenter and the Tukon-Knoop [14] microindenter. Rockwell scales are designated according to load applied and indenting tool used. We have used the E scale,

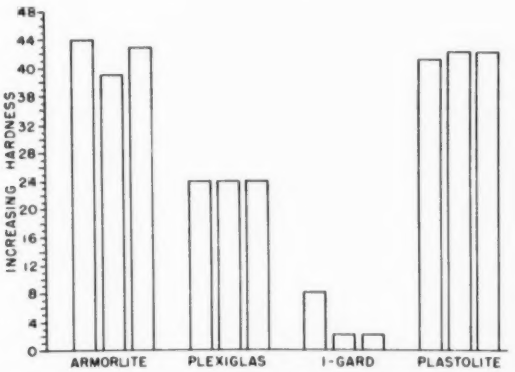

Fig. 3.—Hardness of three samples of each plastic material on the Rockwell E scale. Am. Soc. Testing Materials, Specification D 785-51.

which employs a medium test load (100 kg.) and indenting ball (⅛ in. diameter), particularly suited for softer materials. Tests were made at 76 F. and in accordance with the American Society for Testing Materials specification D 785-51. Hardnesses are reported on three specimens of each material as the arithmetical mean of two to eight tests made on the concave surface of each specimen.[15] Results, in our opinion, indicate (Fig. 3) that Plastolite and Armorlite are of equal Rockwell hardness and much harder than Plexiglas. I-gard specimens were the softest tested.

Knoop tests of the above plastics plus plano samples of borosilicate crown glass, semi-case-hardened (American Optical Company's Temproos) crown glass, and fully case-hardened (American Optical Company's Super Armorplate) safety lenses failed to yield ideal indentations because of surface curvature of the lenses. The

13. Transpex I is produced by Imperial Chemical Industries, Ltd., Hertfordshire, England.

14. Manufactured by Wilson Mechanical Instrument Division of American Chain and Cable Co., Inc., 230 Park Ave., New York 17.

15. Mr. L. S. Churchill and Mr. W. R. McIntosh gave technical assistance in the actual performance of these tests.

results were no more accurate than the verification of the location of these plastics at about 2 on the Mohs scale. The glass specimens gave values between 4 and 5 on the Mohs scale.

THERMOSTABILITY

Two additional specimens of each plastic, checked first by lensometer and Geneva lens measure, were placed on cotton in a water bath at 105 F. for five minutes. After removal they were allowed to cool on a flat surface (concave side down) and were rechecked by lensometer and Geneva lens measure. This procedure was repeated at intervals of 5 degrees (F.) through the boiling temperature. Readings were made in eighths of a diopter and graded plus or minus if they fell between eighths. The laboratory temperature was controlled at 78 F. and the relative humidity at 45%. Plexiglas, Armorlite, and Plastolite showed no deformation at any temperature, including boiling temperatures. I-gard lenses showed changes in surface curvature above 180 F. and gross distortion above 190 F.

IMPACT RESISTANCE

A steel ball ⅞ in. (2.2 cm.) in diameter and weighing 45 gm. was dropped from a height of 50 in. (1.3 meter) onto the apex of new samples of each lens.[16] Four plano samples of I-gard, Armorlite (ophthalmic, rather than industrial thickness), Plastolite, Plexiglas (flat samples 1/16 in. [1.6 mm.] thick), case-hardened borosilicate crown glass (American Optical Company's Super Armorplate), and conventional crown glass were tested. No specimens of Armorlite, Plastolite, or case-hardened crown glass were fractured, but all specimens of Plexiglas, I-gard, and ordinary crown glass were broken. The fragments of I-gard and Plexiglas were larger and less acutely angulated than were the multiple splinters of crown glass.

RESISTANCE TO CHEMICALS

Specimens of each plastic were placed on edge in beakers filled to 1-cm. depth with various chemicals. None of these plastics showed immediate or delayed alteration following such contact with 100-proof ethyl alcohol, 70% isopropyl alcohol, or absolute methyl alcohol for periods of one hour. Similar resistance was shown to carbon tetrachloride (technical) and dilute ammonia solution (household). Tests with acetone showed no effect on Plastolite or Armorlite, but the I-gard lenses were immediately discolored on contact with acetone and began to dissolve within 30 seconds. Plexiglas was only slightly delayed in entering solution with acetone.

Commercial samples of acetone-free nail-polish removers were tested. These are trade-secret mixtures of lacquer solvents containing principally ethyl acetate or amyl acetate (banana oil). Armorlite and Plastolite were, again, found to be resistant, but I-gard lenses showed surface etching after four to six minutes' contact. Plexiglas showed only faint marring after prolonged contact.

16. Specimens were supported horizontally on a wooden tube having an internal diameter of 31 mm. and an external diameter of 40 mm., with a rubber packing washer ⅛ in. in thickness between tube and specimen. The apparatus was manufactured by the Precision Cosmet Co., Inc., Minneapolis. The testing procedure was modified from Federal Specification GGG-G-501 b, Section F 2c (July 13, 1944) by reduction in diameter of the supporting tube, in order to accommodate lenses of smaller diameter.

SUMMARY

Plano samples of Armorlite, I-gard, Plastolite, crown glass, case-hardened glass, and Plexiglas were tested for hardness, inflammability, thermostability, impact resistance, and chemical resistance. Hardness of the plastics centers around 2 on the Mohs scale; that of glass lenses falls between 4 and 5. Rockwell indentation tests showed Armorlite and Plastolite to be much harder than Plexiglas. In our opinion, I-gard was the softest of all specimens tested. Armorlite, Plastolite, and Plexiglas were unaffected by increasing temperatures, including the boiling point at this altitude. I-gard lenses were distorted at temperatures above 180 F. All these plastics are rather difficultly combustible and are slow-burning. Fifty-inch drop-ball tests shattered specimens of I-gard, Plexiglas, and crown glass but failed to break any samples of Armorlite, Plastolite, or case-hardened glass. All lenses resisted attack by common alcohols, carbon tetrachloride, and ammonia. I-gard and Plexiglas rapidly went into solution with acetone and may be damaged by some acetone-free nail-polish removers. Plastolite and Armorlite resisted acetone and the nail-polish removers.

CONCLUSIONS

Two useful and relatively hard types of plastic spectacle lenses are available: the Armorlite lens, in prescription strengths, and the Plastolite lens, in plano strength only. These are thermostabile lenses of light weight, improved resistance to common chemicals, and maximum safety value. They have little tendency toward fogging and are superior to case-hardened glass in resistance to welders' splatter and high velocity particles. The I-gard lens, in our opinion, is relatively soft, is easily affected by heat and some organic solvents, and has less impact resistance than has case-hardened glass or other plastic lenses tested.

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NUTRITIONAL DYSTROPHY OF CORNEAL EPITHELIUM

Preliminary Report of Patients Reacting Favorably to Vitamin Therapy

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LESIONS of the corneal epithelium vary in appearance from minute changes in the individual epithelial cells to massive exfoliations of the whole covering, and in etiology from those with obscure and conjectural causes to those of proved and definite origin.

One of these lesions of the corneal epithelium of a nature and of an origin both obscure and conjectural has lately been observed with increased frequency in ophthalmological practice in the region around Lucena, Quezon Province, Philippines. It appears to be morphologically identical with the lesions of the corneal epithelium described by Ocampo,[1] in 1941, as dystrophy of the corneal epithelium and with noninflammatory lesions of the corneal epithelium which appeared in great numbers in the Philippines during the war years from 1942 to 1944 inclusive.

The report is a clinical study of cases of this lesion seen in private practice within a four-year period and is an attempt to determine their etiologic classification.

Since facilities for confirmatory biochemical and histopathological examinations in these cases have not previously been available, this report is at best a preliminary one. Arrangements, however, have been made for the necessary examinations in the future, and these will be reported in due time.[2]

CLINICAL EXAMINATION

In addition to the routine examination of the external eye, ophthalmoscopy, and tests of visual acuity, retinoscopy and refraction, biomicroscopy, tangent screen scotometry, tests for corneal sensibility, and Schirmer's test were done.

Attention was also paid to the condition of the lips, the tongue, and the integument as part of a general physical examination conducted in all cases, while cutaneous sensibility and the common deep reflexes were tested in the cases in which numbness or a tingling sensation of the extremities was complained of.

INCIDENCE

Number and Sex Incidence.—For the four-year period under review, a total of 44 patients were seen, 31 of whom were females and 13 males, or a ratio of 2.38

Read before the Philippine Ophthalmological and Otolaryngological Society, Manila, Philippines, Sept., 1950.

1. de Ocampo, G.: Epithelial Corneal Dystrophy Due to Hypovitaminosis, Acta med. Philippina **3**:105-123 (July-Sept.) 1941.

2. Nañagas, P. J.: Nutritional Corneal Epithelial Dystrophy: Report of Additional Cases with Biochemical Examinations, read before the Philippine Ophthalmological and Otolaryngological Society, November, 1951, to be published.

females to 1 male. However, insufficient follow-up studies on 3 patients have left only 41 as the actual basis for this study; of these, 27 were females.

Age.—The ages ranged from 16 to 70 years, with an average incidence of 30.2 years. Five patients were aged 20 or below; 22 were between 21 and 30; 10 were between 31 and 40; 2 were between 41 and 50, and 2 were 51 or over.

Incidence of Pregnancy and of Breast Feeding.—Of the 27 females, 8 dated the onset of ocular symptoms to pregnancy, the majority to the last trimester; 9 had the onset while they were nursing the newborn infant.

Other Pertinent Data.—Residence: The patients came from several towns within the immediate vicinity of Lucena.

Occupation: A great many (25) were housewives; 8 were farmers; 3 were students, and 1 was a teacher, 1 a fisherman, 1 a vendor, and 1 a senile, unemployed patient.

Food Habits: With few exceptions, the food habits of the group were uniformly characteristic of those generally observed in the lower bracket of the large middle class of the province, i. e., inadequate in minerals and vitamins.

SYMPTOMATOLOGY

Subjective Ocular Symptoms.—The symptom outstandingly common to all the patients was foggy vision. This term seems preferable to any other because the patients most frequently referred to this disturbance of vision in the vernacular, as *ma-abo-abo,* which means "foggy." This disturbance of vision started insidiously and progressed slowly, generally with simultaneous involvement of the two eyes.

At first examination vision without correction ranged from 20/20— (Case 35) to less than 10/200 (Cases 1 and 24). However, patients with considerable visual loss had contributing, associated visual conditions, such as chronic retrobulbar neuritis. The maximum visual impairment, with refractive errors corrected and without any apparent associated ocular condition, was 20/80 (Cases 8 and 16). It is interesting to note that in the majority of cases the degree of impairment of visual acuity was roughly the same in the two eyes.

Dazzle was the next commonest complaint. Since the patient's intolerance to light was not comparable to that frequently observed in patients with inflammatory lesions of the cornea, such as phlyctenular keratitis, or even to that in patients with xerophthalmia, it did not seem to warrant the term "photophobia." Twenty-seven of the patients observed difficulty in seeing under bright light and preferred the subdued light at dusk to the light at noon. Three patients had more intolerance to light and could be classified as having photophobia (Cases 24, 30, and 34).

Six of the patients had increased lacrimation; two had the sensation of foreign body, and one had itching in the eyes.

None of the patients, on being questioned, admitted of difficulty in seeing at night except the first patient, who had definite signs of xerosis of the conjunctiva and cornea. Pain in the eyes was never mentioned in the anamnesis. Almost all the patients were without a history of previous redness or of discharge from the eyes.

Objective Ocular Symptoms.—Grossly, there might be no observable lesion in the eyes in the early cases; on the other hand, in the more advanced cases, the involvement of the cornea could readily be seen. On focal illumination, this appeared to be in the form of grayish superficial punctate lesions, grouped rather closely in

the pupillary area. The individual lesions varied in size from the barely perceptible to the confluent, pinhead in size, or even larger. They did not appear in the periphery or near the limbus.

There were, as a rule, no signs of inflammation. One patient had associated blepharitis (Case 12), and another had maceration of the external canthi, with slight conjunctival hyperemia and discharge (Case 29). Only one (Case 30) showed definite proliferation of the limbal vessels and superficial infiltration at the terminal

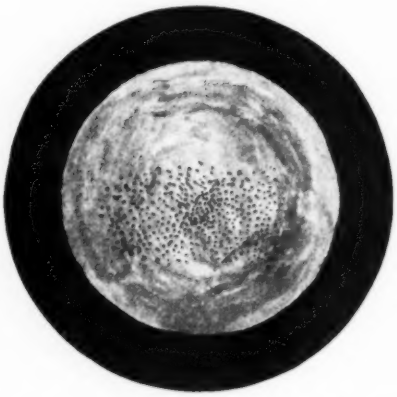


Fig. 1.—Fundus reflex in nutritional dystrophy of the corneal epithelium.

Fig. 2.—Epithelial changes in optic section.

vascular loops. Two patients had pterygium, while one (Case 1) had Bitot's spots (xerosis corneae) in both eyes, and only in this patient could the drying-out phenomenon of Pillat be demonstrated.

Ophthalmoscopic examination at a distance often gave the first indication of corneal abnormality in the early cases. The lesions in the pupillary area appeared as dark punctate areas in the orange-red reflex and might or might not show a definite pattern of distribution (Fig. 1). They might appear evenly distributed or grouped closely into lines (Cases 6 and 19). In some cases the lesions were arranged

loosely into two transverse bands, with a relatively clear intervening space (Case 22). While the corneal periphery was exempt from these lesions on the whole, the lower corneal half was much oftener involved than the upper.

The fundus, where it could be clearly visualized, appeared to show no abnormality, except for pallor of the optic disk in eyes with wide central-field defects (Cases 24 and 36).

With the biomicroscope, the lesions in the early and the fairly early cases were seen to be clearly and solely epithelial, discrete, and limited to single or only a few adjoining epithelial cells. The corneal section (Fig. 2) shows that Bowman's membrane was not involved but that the punctate lesions were slightly raised over the unaffected epithelial cells, standing out rather sharply in this respect. They did not stain with fluorescein.

In the advanced cases, Bowman's membrane disappeared in an extension of the epithelial lesion inward, and in one instance (Case 24) there was wide thinning of the substantia propria, with relative thickening of the epithelial layer. Here, the epithelium appeared brighter and more homogeneous than the normal, and the cells seemed to be piled up or heaped together in irregular mounds in the region of the pupillary area.

Worthy of attention was the appearance of the corneal nerves in these eyes. They seemed thickened and stood out more prominently than in the normal eye. There was no difficulty in locating them or in following them from the limbus centripetally.

Testing for corneal sensibility with a fine hair gave the impression that most of the patients with more advanced disease had hypesthesia of the cornea. Schirmer's test, done on a few patients selected at random, gave normal results, and in those with complaint of lacrimation it showed an increase in the lacrimal secretion.

Scotometric determinations on the Bjerrum tangent screen, using a 1/1000 mm. white test object, revealed either a central or a paracentral scotoma in 8 patients. In three of these (Cases 1, 24, and 40) the scotoma was centrocecal.

Retinoscopy was done in all cases to minimize the effect of possible uncorrected errors of refraction on the evaluation of visual acuity. Refractive errors were few (Cases 1, 18, 19, and 39), however, and in each case correction was made with the corresponding lens before evaluation of the visual acuity.

One patient (Case 18) had phthisis bulbi of one eye, due to an old injury to the globe.

Associated Extraocular Signs and Symptoms.—Twelve patients had numbness of the extremities of the glove-and-sock type of chronic peripheral polyneuropathy, with demonstrable cutaneous hypesthesia in all. The knee jerk was not as reliable an indicator of the presence of peripheral neuropathy as the sensibility tests except in one patient (Case 32), in whom the sign was bilaterally absent. This patient also complained of severe general body weakness. In the other patients the knee jerk was present to a degree not often proportional to the degree of cutaneous hypesthesia.

Cheilosis was next in frequency among the extraocular associated signs. Nine patients presented angular stomatitis at the time of the first examination. Nothing unusual was observed in the tongue and integument in any case.

RESULTS OF THERAPY

On a previous supposition that the lesions of the cornea in these patients might have been due to vitamin-A deficiency, this vitamin was given to several patients in therapeutically high doses (150,000 U. S. P. units daily in three divided doses, by mouth). In Case 1 this dose was administered for three months; in Cases 2 and 8, for one month. In Case 1, in which there were Bitot spots and the drying-out phenomenon was originally elicited, these manifestations disappeared, but vision remained unchanged and the punctate spots retained more or less the same number and distribution as before the institution of treatment. No observable improvement appeared in the other two cases.

In one other case (Case 4) vitamin A was given in similar doses at the onset of treatment and for some six months after, with occasional interruptions. At the end of this time there was very little improvement either in vision or in the corneal lesions; yet with the addition of thiamine hydrochloride U. S. P., 100 mg. daily by intramuscular injection, there was striking improvement in visual acuity on the ninth day, from 20/100 in each eye to 20/60 and 20/40 in the right and left eyes respectively, with a proportionate diminution in the number of punctate spots in the cornea.

In Case 3, in which cheilosis was present, the vitamins of the B complex were given by injection and orally, and recovery of visual acuity, from 20/200 in the right eye and 20/80 in the left eye to 20/20 in each eye, took place in three months. On the basis of this remarkable result with the vitamin B complex, the vitamins of this group became the treatment of choice in the succeeding cases.

Thiamine hydrochloride with vitamin A was of no avail in Case 7, one of advanced pulmonary tuberculosis, and even very high doses of the vitamin B complex were of little use in cases with seemingly irreversible corneal changes, as in Case 24, in which there was thinning of the substantia propria. It was also of little use in restoration of vision in cases of associated irreversible damage to the optic nerve due to retrobulbar neuritis, as in Cases 24 and 36.

In general, however, the effects of the vitamin B complex on this type of corneal disturbance appears to be very satisfactory.

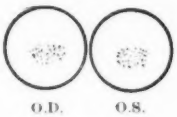
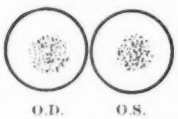
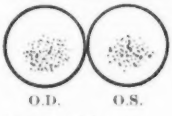
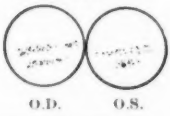
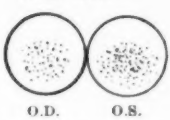
No local medicament was given, and no advice as to changes in the diet was offered, in a crude effort to introduce only one element of therapy at a time, the better to evaluate its effects.

Of course, the question might be raised as to why the vitamins of the B complex were given together, and not the individual vitamins of the group one at a time. On the basis of the concept that the vitamins of the B group always act together and synergistically, and that a deficiency in one alone is less likely to occur than a deficiency in all, I considered the vitamins of the B complex in the category of a single element of nutrition.

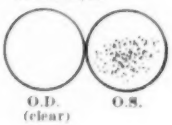
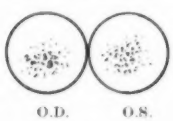
REPORT OF CASES

Several cases typical of the 41 under study are presented.

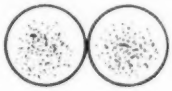
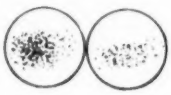
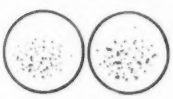
CASE 11.—C. B., a woman aged 21, a housewife, was first seen on June 2, 1948, for the complaint of foggy vision, which she had had for five months. This visual impairment was first noticed by the patient on the second month after her delivery; it appeared simultaneously with eruptions at the corners of the lips. Her only other complaint was that of dazzle, which made vision even poorer under bright light or in direct sunlight. At the time of examination she was still breast feeding her 7-month-old child.

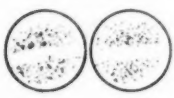
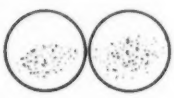
Case No.	Age and Sex	Occupation	Date of First Examination: Visual Acuity; Refraction Diagram of Distribution of Dystrophy Over Cornea	Duration of Visual Disturbance	Other Relevant Data	Treatment and Follow-Up Examination
1	51 M	Farmer	Feb. 22, 1947: V.O.D. 20/80; with +1.50 sph. = 20/40 V.O.S < 20/200  O.D. O.S.	Over 1 yr.	Bitot's spots present in both eyes; pterygium binasally; centrocecal scotoma, 1/1000 white, left	Vitamin A (afaxin®), 150,000 U. daily by mouth until May 16, 1947; Bitot's spots cleared; corneal dystrophy unchanged; vision unchanged
2	29 M	Farmer	Feb. 27, 1947: V.O.D. 20/100; V.O.S. 20/100  O.D. O.S.	4 mo.	Dazzle present; scotoma, paracentral, bilateral; cutaneous hypesthesia over both legs up to knees; all teeth carious	Vitamin A (afaxin®), 150,000 U. daily to March 29, 1947 without improvement
3	27 F	Housewife	Jan. 7, 1948: V.O.D. 20/100; V.O.S. 20/80 O.D. O.S.	1 yr.	Symptoms noticed at 8th mo. of pregnancy; breast feeding; scotoma, central, bilateral; dazzle present; cutaneous hypesthesia over half of both legs; cheilosis present	Vitamin A (afaxin®), 150,000 U., with vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets) Jan. 27, 1948: V.O.D. 20/40—; V.O.S. 20/40; dystrophy less; cutaneous hypesthesia improved March 16, 1948: V.O.D. 20/20; V.O.S. 20/20; no more dystrophy
4	35 F	Housewife	Jan. 16, 1948: V.O.D. 20/140; V.O.S. 20/140 O.D. O.S.	1 mo.	Dazzle present; cutaneous numbness and hypesthesia of both legs; no scotoma demonstrated, owing to inability of patient to maintain attention	Vitamin A (afaxin®), 150,000 U. daily until June 23, 1948 V.O.D. 20/100; V.O.S. 20/100; dystrophy still present Thiamine HCl, 100 mg. parenterally daily, started June 24, 1948 July 1, 1948: V.O.D. 20/60; V.O.S. 20/40—; dystrophy much less
5	24 F	Housewife	Jan. 21, 1948: V.O.D. 20/80; V.O.S. 20/80 O.D.: +0.25 cyl., ax 180  O.D. O.S.	6 mo.	Delivered 3 mo. before; not breast feeding; dazzle present; cutaneous numbness and hypesthesia of glove-and-sock type	Vitamin A (afaxin®), 150,000 U. daily with thiamine HCl, 100 mg. daily Follow-up lost until March 23, 1948 March 23, 1948: Dystrophic areas rare and scattered; V.O.D. 20/20—; V.O.S. 20/20 (Patient claims improvement evident within 20 days after onset of treatment)
6	30 F	Housewife	Feb. 12, 1948: V.O.D. 20/30; V.O.S. 20/30  O.D. O.S.	8 mo.	Breast feeding a 2-mo.-old child; no complaint other than poor vision	Vitamin B complex (betalin®) parenterally for 10 days, with oral administration (basic formula vitamin tablets) March 2, 1948: Cornea clear; V.O.U. 20/20
7	40 F	Housewife	March 27, 1948: V.O.D. 20/80; V.O.S. 20/100  O.D. O.S.	3 mo.	Cutaneous numbness, circumoral and glove-and-sock types; tuberculosis, pulmonary, far advanced, bilateral	Vitamin A (afaxin®) and thiamine HCl, 100 mg. by daily injection April 5, 1948: No change

Data on Cases of Nutritional Dystrophy of Corneal Epithelium—Continued

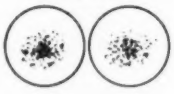
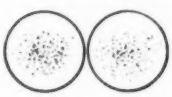
Case No.	Age and Sex	Occupation	Date of First Examination: Visual Acuity; Refraction Diagram of Distribution of Dystrophy Over Cornea	Duration of Visual Disturbance	Other Relevant Data	Treatment and Follow-Up Examination
8	50 F	Housewife	April 1, 1948: V.O.D. 20/40; V.O.S. 20/80 O.D. O.S.	1 mo.	No other complaint	Vitamin A (afaxin®) alone; no improvement up to May 4, 1948; no change in corneal dystrophy
9	24 F	Housewife	May 16, 1948: V.O.D. 20/40; V.O.S. 20/60 O.D. O.S.	3 mo.	Nursing an 8-mo.-old child; cheilosis present	Thiamine HCl, 100 mg. daily; riboflavin, 5 mg. t.i.d. orally; follow-up lost Jan. 14, 1950: Patient consulted me for Morax-Axenfeld conjunctivitis, but with cornea clear; claimed complete recovery of vision after 2 wk. of treatment in 1948
10	25 F	Housewife	May 20, 1948: V.O.D. 20/20; V.O.S. 20/70  O.D. (clear) O.S.	2 mo.	Dazzle present June 7, 1948: O.D. O.S. May 18, 1949: O.D. O.S. Nov. 14, 1950:  O.D. O.S.	Vitamin B complex (betalin®) parenterally for 10 days, with supplemental vitamin B complex by mouth June 7, 1948: V.O.S. 20/40 July 5, 1948: V.O.S. 20/20–3 May 18, 1949: Full-term pregnancy; visual impairment for 2 wk.; vitamin B complex prescribed again Nov. 14, 1949: Breast feeding 5½ mo.-old child; patient claims vision improved on May 25, 1949, after delivery, became normal in 1 wk.; present visual impairment for 2 mo.; vitamin B complex parenterally and orally Dec. 18, 1949: Corneas clear; V.O.U. 20/20
11	21 F	Housewife	June 2, 1948: V.O.D. 20/30; V.O.S. 20/50 O.D. O.S.	5 mo.	Delivered 7 mo. before; breast feeding; dazzle present; cheilosis	Vitamin B complex by injection (betalin®) and orally (basic formula vitamin tablets) Aug. 16, 1948: Cornea clear; V.O.D. and V.O.S. 20/20
12	31 F	Housewife	June 16, 1948: V.O.D. 20/200; V.O.S. 20/200 O.D. O.S.	Dazzle for 7 mo.; foggy vision 1 wk. (?)	Delivered 4 mo. before; breast feeding; dazzle marked; blepharitis, chronic, bilateral; scotoma, central, bilateral; lacrimation present; Schirmer's test showed increased lacrimal secretion	Vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets); sulfathiazole ointment and lid massage June 23, 1948: Blepharitis much improved; V.O.D. and V.O.S. 20/70 June 30, 1948: V.O.D. and V.O.S. 20/20—; dystrophy very slight March 1, 1949: Seen again for recurrence of blepharitis; cornea clear; V.O.D. and V.O.S. 20/20

Data on Cases of Nutritional Dystrophy of Corneal Epithelium—Continued

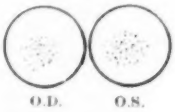
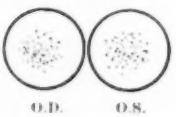
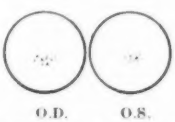
Case No.	Age and Sex	Occupation	Date of First Examination: Visual Acuity; Refraction Diagram of Distribution of Dystrophy Over Cornea	Duration of Visual Disturbance	Other Relevant Data	Treatment and Follow-Up Examination
13	35 F	Housewife	June 16, 1948: V.O.D. 20/70—; V.O.S. 20/70  O.D. O.S.	1 mo.	Dazzle present; no scotoma demonstrable; numbness of glove-and-sock type	Vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets) June 22, 1948: V.O.D. and V.O.S. 20/50— July 1, 1948: V.O.D. and V.O.S. 20/50; corneal dystrophy still present but much less Further follow-up lost
14	24 F	Housewife	Dec. 13, 1948: V.O.D. 20/50; V.O.S. 20/40  O.D. O.S.	4 mo.	Delivered 8 mo. before; nursing; dazzle present; confluence of dystrophic areas in right cornea	Vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets) Jan. 10, 1949: V.O.D. 20/30; V.O.S. 20/20—; cornea practically clear
15	18 M	Student	Dec. 18, 1948: V.O.D. 20/50; V.O.S. 20/50 O.D. O.S.	2 mo.	Dazzle present; sensation of foreign body or grit in eyes	Vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets) June 17, 1950: V.O.D. 20/40; V.O.S. 20/20; claims recovery with treatment, followed by present recurrence of 2 wk.; same treatment instituted as before July 2, 1950: V.O.D. and V.O.S. 20/20; cornea clear
16	17 M	Student	Jan. 8, 1949: V.O.D. 20/60; V.O.S. 20/80 O.D. O.S.	2 mo.	No other complaint	Vitamin A (afaxin®), 150,000 U. orally daily Jan. 22, 1949: V.O.D. 20/60—; V.O.S. 20/80—; vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets) started Feb. 5, 1949: V.O.D. 20/40; V.O.S. 20/60 Feb. 20, 1949: V.O.U. 20/20 July, 1949: V.O.U. 20/20; corneas clear
17	28 M	Farmer	Feb. 2, 1949: V.O.D. and V.O.S. 20/40  O.D. O.S.	6 mo.	Dazzle present; cheilosis; recurrent attacks of chills and fever (malaria) during past year; no scotoma	Antimalarial therapy instituted; vitamin A (afaxin®), 150,000 U. orally a day; treatment continued to April 10 April 10, 1949: Dystrophy unchanged, actually increased; malaria controlled; V.O.D. and V.O.S. 20/200; scotoma now present, central, bilateral; numbness of glove-and-sock type; vitamin B complex started April 20, 1950: Claims to have continued treatment for 1 mo. and then discontinued it; V.O.D. and V.O.S. 20/200; marked pallor of optic disks on both sides; no more dystrophy (Retrobulbar optic neuropathy led to optic nerve atrophy)

Case No.	Age and Sex	Occupation	Date of First Examination: Visual Acuity; Refraction Diagram of Distribution of Dystrophy Over Cornea	Duration of Visual Disturbance	Other Relevant Data	Treatment and Follow-Up Examination
18	36 F	Housewife	Feb. 5, 1949: R.E.: Phthisis bulbi V.O.S. 20/20 (cornea clear) with correction of — 1.00 cyl., ax 180	.....	Seen again Feb. 19, 1949, with dazzle and foggy vision V.O.S., with correction, 20/40 O.S.	Vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets) July 2, 1949: Cornea clear; V.O.S. 20/20, with correction; claims full recovery of vision after 2 wk. of treatment, given Feb. 19, 1949
19	34 M	Fisherman	Feb. 11, 1948: V.O.D. 20/70; with +1.50 sph. = 20/30— V.O.S. 20/50—; with +0.50 sph. = 20/50 O.D. O.S.	9 mo.	Dazzle present	Vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets) Feb. 26, 1949: V.O.D., with correction, 20/30; V.O.S., with correction, 20/40; less atrophy March 8, 1949: V.O.D., with correction, 20/20; V.O.S., with correction, 20/20; no more dystrophy
20	38 M	Farmer	Feb. 19, 1949: V.O.D. 20/40; V.O.S. 20/30 O.D. O.S.	3 mo.	Pterygium present, right eye	Vitamin A (afaxin®), 150,000 U. daily until Feb. 26, 1949, when V.O.D. was 20/70 and V.O.S. 20/30, with dystrophy thicker on right; vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets) started Feb. 26 March 3, 1949: V.O.D. 20/30 and V.O.S. 20/30—; still with some dystrophy Further follow-up lost
21	23 F	Housewife	Feb. 26, 1949: V.O.D. 20/30; V.O.S. 20/50 O.D. O.S.	1 yr.; at times better, at times worse	Delivered 1 yr. before; breast feeding; dazzle; lacrimation and sensation of sand in eyes; cheilosis present	Vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets) started May 16, 1949: Both corneas clear; V.O.D. and V.O.S. 20/20
22	18 F	Housewife	March 16, 1949: V.O.D. 20/30; V.O.S. 20/30  O.D. O.S.	6 mo.	Delivered 8 mo. before; breast feeding; dazzle present Note: Dystrophy extensive, spots grouped in two bands, but with pupillary areas of both eyes practically free	Vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets) March 26, 1949: Dystrophy much less; V.O.D. and V.O.S. 20/20— March 30, 1949: Cornea clear; V.O.S. and V.O.D. 20/20
23	30 M	Farmer	March 21, 1949: V.O.D. 20/30—; V.O.S. 20/40—  O.D. O.S.	1 mo.	Dazzle present	Vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets) April 4, 1949: Dystrophy much less; V.O.D. 20/20—; V.O.S. 20/30 O.D. O.S. Follow-up lost

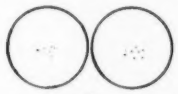
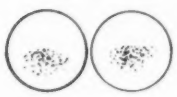
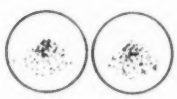
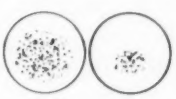
Data on Cases of Nutritional Dystrophy of Corneal Epithelium—Continued

Case No.	Age and Sex	Occupation	Date of First Examination; Visual Acuity; Refraction Diagram of Distribution of Dystrophy Over Cornea	Duration of Visual Disturbance	Other Relevant Data	Treatment and Follow-Up Examination
24	26 F	Housewife	April 11, 1949: V.O.D. < 10/200; V.O.S. < 20/200  O.D. O.S. (Central lesions appear as whitish sheet grossly) Diagram of corneal section seen with biomicroscope, showing absence of Bowman's membrane, heaping of epithelial cells; thinning of substantia propria	9 yr.	During last 9 yr. had been breast feeding 3 children up to 1 yr. of age; large centrocecal scotoma, bilateral, not proportionate to extent of corneal lesions; photophobia and lacrimation present; numbness of glove-and-sock type	Vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets) April 14, 1949: V.O.D. 20/200; V.O.S. 20/70 April 20, 1949: Same as April 14 May 2, 1949: V.O.D. 20/200 and V.O.S. 20/50—2 June 8, 1949: Treatment discontinued; corneal lesion with permanent central macula June 23, 1950: Breast feeding of 3-mo.-old baby resumed; V.O.D. 20/200; V.O.S. 10/200; vitamin B complex resumed; corneal lesions as of May 2, 1949 July 22, 1950: Vision unchanged Note: Permanent optic atrophy secondary to previous retrobulbar optic neuropathy
25	25 F	Housewife	April 18, 1949: V.O.D. 20/30; V.O.S. 20/40 O.D. O.S.	2 mo.	Breast feeding 4-mo.-old child; dazzle present; cheilosis	Vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets) May 2, 1952: Letter received from patient claiming complete recovery of vision; no personal check-up possible
26	40 F	Housewife	April 20, 1949: V.O.D. and V.O.S. 20/70  O.D. O.S.	On and off for 14 yr.; recurrence after each delivery; present visual defect 6 mo.	Dazzle present; numbness of glove-and-sock type; no scotoma elicited	Vitamin B complex parenterally (betalin®) with 50 mg. of thiamine HCl added, plus vitamin B complex orally May 23, 1949: V.O.D. and V.O.S. 20/50; dystrophy much less June 4, 1949: V.O.D. 20/30; V.O.S. 20/20—; practically no more dystrophy
27	40 M	Vendor	April 25, 1949: V.O.D. 20/30; V.O.S. 20/20— O.D. O.S.	1 wk.	Pyorrhea, advanced	Removal of all teeth advised; vitamin B complex parenterally and orally June 13, 1949 (after 1 mo. of treatment): Cornea clear; V.O.D. and V.O.S. 20/20
28	17 M	Farmer	May 19, 1949: V.O.D. 20/30; V.O.S. 20/30 O.D. O.S.	3 wk.	Dazzle present; pneumonia 1 mo. before, followed by recurrence of chronic malaria	Antimalarial therapy plus vitamin B complex parenterally and orally June 1, 1949: Corneas clear; V.O.D. and V.O.S. 20/20

Data on Cases of Nutritional Dystrophy of Corneal Epithelium—Continued

Case No.	Age and Sex	Occupation	Date of First Examination: Visual Acuity; Refraction Diagram of Distribution of Dystrophy Over Cornea	Duration of Visual Disturbance	Other Relevant Data	Treatment and Follow-Up Examination
29	27 F	Housewife	June 6, 1949: V.O.D. 20/40; V.O.S. 20/40  O.D. O.S.	3 wk.	Dazzle present; maceration of both external canthi, with mucoid discharge	Vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets); zinc sulfate, 0.5% as drops for both eyes June 29, 1949: Cornea with much less dystrophy; V.O.D. and V.O.S. 20/20 (some) June 30, 1949: Corneas clear; V.O.D. and V.O.S. 20/20
30	24 F	Teacher	July 9, 1949: V.O.D. 20/70; V.O.S. 20/50— O.D. O.S. Neovascularization from limbal vessels present at 7 to 9 o'clock on right; 4 to 5 o'clock on left	3 yr., intermittently	Photophobia marked; lacrimation; no cheilosis Note: One sister with corneal neovascularization and cheilosis without corneal dystrophy, not included in this series	Vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets) July 18, 1949: V.O.D. 20/50—; V.O.S. 20/40—; dystrophy much less July 31, 1949: V.O.D. 20/40; V.O.S. 20/30—; dystrophy clearing from top downward Aug. 21, 1949: V.O.D. and V.O.S. 20/30 Oct. 6, 1949: V.O.D. 20/30; V.O.S. 20/30, with +0.50 cyl., ax 90 = 20/20—; cornea clear; neovascularization receded
31	30 F	Housewife	Oct. 7, 1949: V.O.D. 20/70; V.O.S. 20/50 O.D. O.S.	2 mo.	Cheilosis present	Vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets) Patient could not be contacted afterward until April 3 April 3, 1950: Corneal dystrophy much less, but vision unchanged; treatment not followed regularly; same treatment prescribed as before and followed strictly April 14, 1950: V.O.D. and V.O.S. 20/20; no more dystrophy
32	16 M	Student	July 10, 1949: V.O.D. 20/50; V.O.S. 20/50 O.D. O.S. Note: Vesicle about 1 mm. diameter in left cornea, indicated by circle	4 mo.	Dazzle present; paracentral scotoma of 2° bilaterally; lacrimation; cheilosis; knee jerks both absent; general body weakness Note: Patient had been stinting on food, at times eating nothing but rice and a little salted fish	Vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets) Aug. 1, 1949: General physical condition much improved; V.O.D. 20/30+; V.O.S. 20/20; only very slight dystrophic changes left in right cornea; cheilosis gone
33	43 M	Farmer	July 29, 1949: V.O.D. and V.O.S. 20/40  O.D. O.S.	1½ mo.	No associated symptoms complained of	Vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets) Aug. 18, 1949: Dystrophy cleared in upper portion of corneas, thus:  O.D. O.S. V.O.D. and V.O.S. 20/20—Further follow-up not possible

Data on Cases of Nutritional Dystrophy of Corneal Epithelium—Continued

Case No.	Age and Sex	Occupation	Date of First Examination: Visual Acuity; Refraction Diagram of Distribution of Dystrophy Over Cornea	Duration of Visual Disturbance	Other Relevant Data	Treatment and Follow-Up Examination
34	25 F	Housewife	Aug. 27, 1949: V.O.D. and V.O.S. 20/50 O.D. O.S. Note: Small superficial ulcer involving only epithelial layer, indicated by circle; stained with fluorescein	5 mo.	Nursing a 1-mo.-old child; photophobia	Vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets) Sept. 8, 1949: Ulcer healed; dystrophy minimal  O.D. O.S. V.O.D. and V.O.S. 20/20—
35	70 M	Jobless, senile man	Aug. 31, 1949: V.O.D. 20/30; V.O.S. 20/20— O.D. O.S.	1 mo.	Sensation of grit in both eyes	Vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets) Sept. 14, 1949: Corneas both clear; V.O.D. and V.O.S. 20/20—
36	29 F	Housewife	Oct. 27, 1949: V.O.D. 20/100; V.O.S. 20/100 O.D. O.S.	1 yr.	Since delivery, 1 yr. before, had been breast feeding child; dazzle and lacrimation; central scotoma of 3° bilaterally; cheilosis Note: Element of retrobulbar optic neuropathy explains disproportion between amount of dystrophy and visual impairment	Vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets) Patient advised to wean child Nov. 3, 1949: V.O.D. 20/70; V.O.S. 20/100 Nov. 11, 1949: V.O.D. and V.O.S. 20/70; dystrophy no longer present Nov. 21, 1949: V.O.D. 20/40; V.O.S. 20/40— Further follow-up lost
37	25 F	Housewife	Nov. 9, 1949: V.O.D. and V.O.S. 20/40  O.D. O.S.	10 mo.	Condition started at 7th mo. of pregnancy; patient nursing 8-mo.-old child	Vitamin A, 150,000 U. daily, given orally Nov. 16, 1949: No change; vitamin B complex parenterally and orally prescribed Dec. 8, 1949: Corneas clear; V.O.D. and V.O.S. 20/20
38	29 M	Farmer	Nov. 18, 1949: V.O.D. 20/70; V.O.S. 20/50  O.D. O.S.	2 wk.	Dazzle present	Vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets) Dec. 2, 1949: Condition much improved; dystrophy present only inferiorly; V.O.D. 20/40; V.O.S. 20/30 Dec. 12, 1949: Corneas clear; V.O.D. 20/30—; V.O.S. 20/20
39	33 F	Housewife	Nov. 30, 1949: V.O.D. and V.O.S. 20/70 Refraction: V.O.D. with plane = 20/70 V.O.S. with + 1.50 sph. ⊂ + 0.50 cyl., ax 180 = 20/50	8 mo.	Noticed visual impairment at full term; dazzle present  O.D. O.S.	Vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets) Dec. 10, 1949: V.O.D. 20/70; V.O.S. 20/50 (with correction); dystrophy much less; breast feeding continued Feb. 25, 1950: V.O.D. 20/20; V.O.S. 20/20— (with correction); corneas clear

Data on Cases of Nutritional Dystrophy of Corneal Epithelium—Concluded

Case No.	Age and Sex	Occupation	Date of First Examination: Visual Acuity; Refraction Diagram of Distribution of Dystrophy Over Cornea	Duration of Visual Disturbance	Other Relevant Data	Treatment and Follow-Up Examination
40	30 F	Housewife	Dec. 5, 1949: V.O.D. and V.O.S. 20/100— O.D. O.S.	2 wk.	Breast feeding 8-mo.-old child; dazzle present; temporal side of disk pale bilaterally; centrocecal scotoma bilaterally; numbness of extremities of glove-and-sock type	Vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets) Dec. 12, 1949: Numbness much improved; dystrophy less; V.O.D. and V.O.S. 20/70 Jan. 8, 1950: Corneas practically clear; V.O.D. and V.O.S. 20/40 Jan. 18, 1950: Both corneas clear; pallor of temporal side of disk disappeared; V.O.D. and V.O.S. 20/30
41	30 F	Housewife	July 3, 1949: V.O.D. and V.O.S. 20/50 O.D. O.S.	3 mo.	Formication and numbness of feet and hands	Vitamin B complex parenterally (betalin®) and orally (basic formula vitamin tablets) July 14, 1949: Corneas practically clear; V.O.D. and V.O.S. 20/30 July 24, 1949: Corneas clear; V.O.D. and V.O.S. 20/20

Ocular examination showed fine stipplings of the superficial layer of each cornea closely grouped around the pupillary area; these were further localized by the biomicroscope to the corneal epithelium, with Bowman's membrane intact. Vision was 20/30 in the right eye and 20/50 in the left eye. There was no refractive error and no scotoma.

The only pertinent extraocular physical finding was cheilosis.

She was given vitamin B complex by daily injection [3] for 10 days, supplemented by oral administration of tablets of the complex [4] twice daily. This treatment was carried on for 2½ months.

At the last examination, on Aug. 16, 1948, both corneas were clear, and vision was 20/20 in each eye.

CASE 37.—G. S., a woman aged 25, a housewife, was first seen on Nov. 9, 1949, for foggy vision, of 10 months' duration. The visual impairment was first noticed in the seventh month of her last pregnancy and continued, with slight deterioration after delivery, while breast feeding her child. No other complaint could be elicited.

Ocular examination showed fine stipplings on the superficial layers of the cornea, occupying the lower three-fourths of the pupillary area and closely grouped into a circle of about 4-mm. diameter. There was no inflammatory sign. Vision was 20/40 in each eye. The refractive error was only 0.25 D. sph. for each eye. There were no pertinent extraocular findings.

She was given vitamin A by mouth (150,000 units daily) for one week, but reexamination, on Nov. 16, 1949, showed that the corneal lesion and the vision were unchanged. Vitamin B complex was given by daily injection for 10 days, with supplemental oral administration of the complex. This treatment was continued to the date of the last examination, on Dec. 3, 1949, when both corneas were practically clear, with vision of 20/20— in each eye.

3. The daily injection dose of vitamin B complex which was used in all these cases consisted of thiamine hydrochloride, 10 mg.; riboflavin, 4 mg.; nicotinamide, 150 mg.; pantothenic acid, 5 mg., and pyridoxine hydrochloride, 10 mg. (betalin®).

4. The vitamin B complex tablets administered in all these cases supplied, per tablet, 10 mg. of thiamine hydrochloride, 5 mg. of riboflavin; 150 mg. of nicotinamide, and 150 mg. of ascorbic acid (Squibb basic formula vitamin tablets, now known as vitretin®).

The following case is atypical in the sense that it involved only one eye and was followed by recurrences.

CASE 10.—C. P., a woman aged 25, a housewife, was first seen on May 20, 1948, with the complaint of foggy vision in the left eye. This was noticed two months previously, was insidious in onset, progressive, but unaccompanied by any other symptom. No obstetrical history was given. On examination, the only relevant findings were in the eyes. The right eye was normal in all respects: the cornea was clear, the fundus reflex and the fundus were normal, and vision was 20/20. The left eye showed fine punctate lesions roughly occupying the lower half of the pupillary area. She was given vitamin B complex by injection for 10 days, with supplemental oral administration of 2 tablets daily.

On June 7, 1948, there were noticeably fewer punctate lesions, and by July 5 the cornea was clear, with vision of 20/20 — 3 in that eye.

She was again seen May 18, 1949, pregnant and at full term, with a complaint of having had foggy vision in both eyes for two weeks. Both eyes then showed fine punctate lesions in the cornea, distributed rather loosely over the lower half of the orange-red reflex when the pupil was dilated 4 mm. Vision was 20/40 in each eye. Vitamin B complex was given parenterally and orally. The patient was lost track of until Nov. 14, 1949, when she claimed that after delivery, on May 25, vision remained foggy for a week but that at the end of that time vision rapidly improved to normal. On this date, Nov. 14, while breast feeding a 5½-month-old child, she again noticed foggy vision for two months, for the third time. Both eyes again showed the superficial punctate lesions of the cornea loosely covering the whole pupillary area. Vision was 20/50 in the right eye and 20/70 in the left eye. High doses of vitamin B complex (two daily injections instead of one) with supplemental oral administration were given. On Dec. 18, 1949, the corneas were clear, and vision was 20/20 in each eye.

The next case is one with associated retrobulbar optic neuropathy, probably also of nutritional origin.

CASE 36.—M. P., a woman aged 29, a housewife, was first seen Oct. 27, 1949, with the complaint of very foggy vision, numbness of the extremities, lesions at the corners of the lips, dazzle, and lacrimation. The symptoms had appeared immediately after delivery, a year before, and had progressed rapidly. She had been breast feeding her one-year-old child up to this time. Examination showed superficial punctate lesions of the pupillary area of each cornea, shown with the biomicroscope to be limited to the epithelium. Vision was 20/100 in each eye. She had bilateral central scotoma for form (1/1000 test object) of 3 degrees and increased lacrimation (Schirmer's test). She presented cheilosis, but the limbal vessels did not show any proliferation. A diagnosis of nutritional dystrophy of the corneal epithelium and nutritional retrobulbar optic neuropathy was made, and vitamin B complex was given by injection and orally. She was advised to wean the child. On Nov. 3, 1949, vision was 20/70 in the right eye and 20/100 in the left eye (injections of the vitamin had not been carried out regularly). On Nov. 11, vision was 20/70 in each eye, the corneas were both clear, and the cheilosis had disappeared. The numbness had improved considerably. The patient failed to report for follow-up study and could not be contacted, owing to change of residence.

COMMENT

It is apparent that these cases are instances of a definite affection of the cornea of a nature of, and with an etiology closely related to, a nutritional defect—more specifically, a vitamin deficiency. Duke-Elder [5] mentioned certain types of epithelial degeneration characterized by small lesions in the corneal epithelium, of obscure origin, which he considered to be degenerative, possibly with the added factor of neuropathy. More specifically, Kirwan [6] described corneal degeneration accompany-

5. Duke-Elder, W. S.: Text-Book of Ophthalmology, Vol. 2, St. Louis, C. V. Mosby Company, 1946.

6. Kirwan, E. W. O.: Tropical Ophthalmology, in Stallard, H. B., Editor: Modern Practice in Ophthalmology, 1949, New York, Paul B. Hoeber, Inc., 1949.

ing retrobulbar neuritis in cases of tropical vitamin-B-complex deficiencies with minute superficial punctate spots in the cornea, which might or might not ulcerate. However, neither author gave any further details.

In 1933, Ayuyao [7] described corneal lesions observed in beriberi which may have been identical with the lesions in the present series of cases, and thereby he appears to have been the first to report cases of corneal lesions associated with thiamine deficiency locally. Ocampo,[1] in 1941, identified similar corneal lesions as dystrophy of the corneal epithelium and ascribed them principally to hypovitaminosis A; in 1943, among other ocular symptoms and signs associated with the severe multiple-vitamin deficiencies observed in the Philippines during those war years, Fernando and associates [8] included lesions of the cornea which appeared to be of the same type and nature as those in the present series.

A review of the three cases reported by Ayuyao and of the five cases reported by Ocampo reveals the striking fact that definite signs and symptoms of polyneuropathy were exhibited in all these cases except one of Ocampo's. Similarly, in two other cases with the same type of corneal lesions presented by the Department of Eye, Ear, Nose, and Throat Diseases of the Philippine General Hospital in several weekly clinical conferences,[9] numbness and tingling sensations of the extremities were complained of. In 12 of my own cases cutaneous hypesthesias and paresthesias were present. This much can be deduced therefrom: These patients were suffering from thiamine deficiency.

It may be mere coincidence that all Ayuyao's three cases were of women in the last trimester of pregnancy; in eight of my own cases ocular symptoms developed during the last trimester of pregnancy, and in nine other cases, the onset was while the women were breast feeding their babies. In the majority of these cases there was associated polyneuropathy. In the Philippines at least, it is seldom that one associates increased incidence of Bitot's spots with pregnancy. Subclinical vitamin-A deficiency may occur, but not outright manifestations of the deficiency, such as xerosis conjunctivae et corneae, hyperkeratoses of the skin, and night blindness. In pregnancy and lactation, the times in a woman's life in which the greatest demand for vitamins exists, the commonest manifestations of deficiency are those of the vitamin B complex, rather than those of the oil-soluble groups. By inference, therefore, it would seem that any manifestation of deficiency exhibited during these periods was more likely to belong to the vitamin B group than to any other.

Even the factor of age has much to do with the etiology. All the cases so far encountered, and those in the local literature, were of adults. The youngest patient in the present series was 16 and the average age was 30. Vitamin-A deficiency manifests itself most frequently in infants and children, for the reason that their vitamin-A reserves are very low. The liver of infants and children contains only about 14 to 17 units of vitamin A per gram, in contrast to an average of 220 units

7. Ayuyao, C. D.: Corneal Lesion in Beriberi, J. Philippine M. A. **13**:158-161 (March) 1933.

8. Fernando, A. S.; Ayuyao, C. C., and Cruz, J. N.: Ocular Symptoms and Signs Associated with Multiple Vitamin Deficiency, Conference on Medical Sciences, Manila, Dec. 21, 1943.

9. Weekly Clinical Conference Reports of the Philippine General Hospital, Manila, Philippine Islands.

per gram for healthy adults.[10] Moreover, the vitamin-A requirements of infants and children are higher (6,000 to 8,000 units daily) than those of adults (1,400 to 2,000 units daily). On the other hand, the capacity of the human body to store vitamin B complex is limited. In adults, therefore, manifestations of deficiency in the B complex group is more likely to appear than those of vitamin-A deficiency.

In a nutritional survey conducted in Bataan, Philippines, by Burch and associates,[11] in which 202 persons were examined, three-fourths of whom had been classified by an earlier clinical survey as having symptoms of beriberi and one-fourth of whom had no such symptoms, while the thiamine blood level, together with the amounts of other nutrients in the blood or serum, such as the serum protein content, was very low, vitamin A levels were normal. The presence of normal levels of vitamin A in the blood of Filipino adults is attributed to their fairly liberal consumption of fish. Ocular manifestations of vitamin-A deficiency in Filipino adults, therefore, is less likely to appear than those of deficiency in the vitamin B complex.

Case 1 of this series was characterized by the occurrence of lesions of the corneal epithelium in the presence of Bitot's spots and the drying-out phenomenon of Pillat. That vitamin A given orally eliminated the last two manifestations without any apparent effects on the first seems to show a difference in their etiology. Moreover, most of the patients in this series improved under treatment with vitamin B complex alone. This may be taken to mean that the corneal lesions are in part due to a deficiency in this group of vitamins, and the effects of their administration may be considered to be in the nature of a therapeutic test.

That the deficiency in vitamin B complex is not the only factor concerned in the production of these lesions of the corneal epithelium is very likely. Multiple dietary deficiencies are oftener the rule than the exception; the attempt to pinpoint deficiency in a single vitamin or a single element of nutrition as the only cause is likely to end in failure. It is more probable that this lesion of the corneal epithelium appears only in persons with moderate to severe deficiency in the vitamin B complex, but that some other etiologic factor is necessary to precipitate the onset of lesions. This explains in part why not all who exhibit deficiency in the B complex vitamins have this lesion in the corneal epithelium, while all patients with such lesions of the corneal epithelium exhibit deficiency in the vitamin B complex.

It may be supposed that the epithelial lesion is based on a neuropathy, since vitamins of the vitamin B group, such as thiamine and riboflavin, are concerned with the maintenance of health of the nerve tissues. The association of a retrobulbar optic neuropathy, as evidenced by the presence of a central-field defect in 8 of the 41 cases, with recovery in most of them with the administration of vitamin B complex is additional evidence that strengthens this supposition. In tropical countries where polished rice (deficient in vitamin B complex) is the staple food, patients who are amblyopic with central-field defects, indicating retrobulbar optic neuropathies or "neuritis," are considered to have a thiamine deficiency and the condition is successfully treated as such (Kirwan[6]; Ocampo and associates[12]). A similar

10. The Vitamins: A Symposium Arranged Under the Auspices of the Council on Pharmacy and Chemistry and the Council on Foods of the American Medical Association, Chicago, American Medical Association, 1939.

11. Burch, H. B.; Salcedo, J.; Carrasco, E.; Intengan, C. L., and Caldwell, A. B.: Nutrition Survey and Tests in Bataan, Philippines, J. Nutrition **42**:9-29 (Sept.) 1950.

12. de Ocampo, G.; Yambao, C. V.; Nañagas, P. J., and Sevilla, C. L.: Epidemic Retrobulbar Neuritis in the Philippines During the Japanese Occupation, Am. J. Ophth. **30**:698-704 (June) 1947.

neuropathy affecting the trigeminal nerve may so interfere with the efferent impulses which normally influence the metabolism of the corneal epithelium as to produce degenerative changes in this tissue, and this explains the existence of circumoral numbness in some cases. The appearance of minute corneal lesions and vesiculations in injuries or surgical resections of the Gasserian ganglion has been described (Pannabecker [13]). These have been attributed not entirely to the resulting anesthesia of the cornea, with its greater chance of injury, but also to a disturbance in the metabolism of the epithelial cells. Similarly, lesions of the corneal epithelium may result from neuropathies involving the trigeminal nerve due to hypovitaminosis.

If, as has been postulated above, there are degenerative changes in the epithelial cells, and this degeneration is due to faulty metabolism in the cells from interference in the normal efferent impulses which govern cellular metabolism, the term "dystrophy" may be considered appropriate for this condition. Doggart [14] may be cited in a passage which applies to the problem in hand. He stated:

> Metabolic disorder, endocrine derangement and nutritional defects together account for a multitude of dystrophic corneae, not only as prime causes, but also as aggravating factors, in which role they frequently overlap. Perhaps the most satisfactory and clear-cut instances are those in which dosage with the appropriate substance swiftly resolves the lesion.

For these corneal lesions, therefore, the following nomenclature is suggested, "nutritional dystrophy of the corneal epithelium"—"nutritional" for the cause, "dystrophy" for the nature, and "corneal epithelium" for the location.

SUMMARY

Forty-one cases are presented as the basis of a study to determine the nature and etiology of certain lesions of the corneal epithelium apparently related to deficiency in the vitamin B group.

Preliminary results of the study appear to bear out the assumption of a definite relation to a deficiency in the vitamin B complex and are highly suggestive of a dystrophic nature.

Further investigations, especially biochemical studies, for determination of the vitamin levels and the contents of other nutritive elements of the blood, and histopathological studies, for determination of the nature of changes in the cells, are warranted before a more definite conclusion can be reached.[15]

13. Pannabecker, C. L., cited in The 1943 Year Book of Eye, Ear, Nose, and Throat, Edited by L. Bothman, and others, Chicago, Year Book Publishers, Inc., 1943.

14. Doggart, J. H.: Corneal Dystrophy, Ophth. Soc. Australia, **9**:122-138, 1949.

15. Arrangements have been made for biochemical examinations of the blood in subsequent cases with the Republic of the Philippine Institute of Nutrition, Manila. These cases are the basis of a second report, which is being prepared for publication.

Annual Reviews

DISEASES OF THE RETINA

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OUTLINE

Retrolental Fibroplasia
- Histopathology
- Incidence and Clinical Course
- Etiology
- Treatment
- Summary and Comment

Retinal Tumors
- Retinoblastoma
- Angiomatosis Retinae

Hypertension
- Treatment

Atherosclerosis
Retinal Vascular Tone
Retinal Vein Occlusion
Diabetic Retinopathy
Toxemia of Pregnancy
Retinal Changes in General Medical Disease
Tapetoretinal Degeneration
Macular Lesions
Retinal Detachment
Trauma

RETROLENTAL FIBROPLASIA

DURING the 10 years which have elapsed since Terry [1] first described retrolental fibropasia, this disease has become the most frequent cause of blindness in children. Much has been learned about its clinical course, incidence, and pathology, but the etiology and treatment of this malady remain unsettled issues.

Several excellent reviews of this subject have been published during the past year, three of which are especially worth noting. Zacharias [2] has compiled a very complete bibliography from a review of 219 communications. Von Winning [3] summarizes the nature of the disease, tabulates its incidence in the Netherlands, and discusses its differentiation from other types of glioma. An informal meeting of pediatricians and ophthalmologists is reported in which the pathology, incidence, etiology, and treatment of the disease and plans for organization of a cooperative survey were discussed.[4]

Histopathology.—The most concrete advance in the knowledge of retrolental fibroplasia during the past year stems from a study of early pathological specimens. It is seldom possible to obtain eyes for pathological study early in the disease which have been observed clinically, for if a premature infant survives initial postnatal

From the Division of Ophthalmology, Department of Surgery, Stanford University School of Medicine.

1. Terry, T. L.: Extreme Prematurity and Fibroblastic Overgrowth of Persistent Vascular Sheath Behind Each Crystalline Lens: I. Preliminary Report, Am. J. Ophth. **25**:203, 1942.

2. Zacharias, L.: Retrolental Fibroplasia: A Survey, Am. J. Ophth. **35**:1426, 1952.

3. von Winning, C. H. O. M.: Retrolental Fibroplasia and the Other Forms of Pseudoglioma, Thesis, The Hague, Netherlands, 1952.

4. M & R Laboratories, Pediatrics Research. Second Conference on Retrolental Fibroplasia, New York, New York University, April 28, 1951.

life his chances for continued existence are usually excellent. Friedenwald, Owens, and Owens [5] and Reese and his co-workers [6] have, fortunately, been able to secure material of this type and have reported it. The course of the disease from its earliest histologically observable manifestation to the formation of a complete retrolental membrane is described by Friedenwald, Owens, and Owens.[5] Their observations are based on a study of 17 eyes, from 10 patients.

The earliest pathological changes are found in the nerve fiber layer of the retina. In localized areas the capillary endothelium shows marked proliferation, producing varicose dilatations and abnormal budding of the vessels. The proliferated capillary endothelial cells show abundance of cytoplasm, which is often basophilic, and large, pale-staining nuclei. Surrounding the areas of endothelial proliferation are increased numbers of glial cells. These cells have darkly staining, spindle-shaped nuclei and are arranged in rows parallel to the retinal surface. In some areas the proliferated endothelial cells are arranged in whorls that resemble glomerular tufts. Occasionally small hemorrhages and areas of edema are noted in the nerve fiber layer, but there is no evidence of inflammatory reaction or destruction of tissue. Müller's fibers are pushed aside, rather than being destroyed, and the ganglion cells remain intact.

As the disease progresses, the nerve fiber layer becomes thickened to many times its normal size by extensive glial, capillary, and fibrous proliferation. Newly formed capillary strands with thin, delicate fibrous stroma extend through the internal limiting membranes, course along the surface of the retina, and branch into the vitreous, producing a picture resembling retinitis proliferans. Small hemorrhages are seen in the retina, along its surface, and in the newly formed tissue, extending into the vitreous. Even in these specimens the outer layers of the retina show no change, the ganglion cells are intact, and the inner plexiform layer is not disturbed.

With progress of the disease, the retina is detached in small folds, which are bridged across by a vascular meshwork at the summit of the detached areas. Numerous branches of the newly formed vessels extend into the vitreous toward the axial portion of the eye and the retrolental space.

In the end-stage disorganization is so extensive that the mass of tissue in the vitreous is difficult to distinguish from that found in other diseases with detachment and disorganization of the retina. However, even in some of these late cases the fibrotic remnants of the intraretinal whorls can still be recognized.

In the eyes of an infant which had shown regression from the acute phase of the disease without extensive destruction of the retina, localized areas of scarring were found in the nerve fiber layer. Again, the typical whorl formation of the proliferated capillary endothelium was noted in the nerve fiber layer.

It was impossible to determine whether the small retinal hemorrhages and localized areas of edema preceded or followed the proliferation of the retinal capillaries. In the earliest cases abnormal capillary proliferation was noted in regions which contained no hemorrhage or extravascular blood pigment. This did not rule out the possibility, however, that minute previous hemorrhages may have been completely absorbed and that the vascular and glial proliferation may have been

5. Friedenwald, J. S.; Owens, W. C., and Owens, E. U.: Retrolental Fibroplasia in Premature Infants: III. Pathology of the Disease, Tr. Am. Ophth. Soc. **49**:207, 1951.

6. Reese, A. B.; Blodi, F. C., and Locke, J. C.: Pathology of Early Retrolental Fibroplasia: An Analysis of the Histologic Findings in the Eyes of Newborn and Stillborn Infants, Am. J. Ophth. **35**:1407, 1952.

a response to hemorrhage. In the more advanced cases in which the new-formed tissue extended into the subhyaloid area or into the vitreous, hemorrhages were usually observed.

It is well known that in early embryonal development the retina is devoid of intrinsic blood vessels. At a later date, capillaries invade the retina by budding off from the central artery and vein in the region of the optic disk. Studies were made of this process of normal vascularization of the retina by examining the eyes of premature stillborn infants to see whether it differed from that found in retrolental fibroplasia. Sprouting capillaries and accompanying glial proliferation were found in the retinas of these eyes, but they had an orderly arrangement, and capillary whorls, which resembled glomerular tufts, were entirely lacking in this normal process. The number and distribution of glial cells in the retina approached, but did not exceed, that normally found in full-term infants or in adults.

In 7 of the 10 cases reported in detail autopsies were performed. Microscopic studies of the viscera in these cases failed to reveal any lesions in the internal organs which appeared to be related to the retinal disease.

Reese, Blodi, and Locke[6] report the microscopic findings in the eyes of 10 premature infants with retrolental fibroplasia who survived from 41 to 125 days after birth. Prior to death, the eyes of each patient were examined repeatedly with the ophthalmoscope through dilated pupils, and the presence of early retrolental fibroplasia was definitely established. The duration of the disease in these patients varied from 7 to 48 days. Excellent photomicrographs of the retinal lesions are included in the article.

The histological changes in these 20 eyes with retrolental fibroplasia confirm in many details those described by Friedenwald and his co-workers. The process is at first confined to the nerve fiber layer of the retina in the equatorial region. It consists of diffuse thickening of this layer, due to edema and to small nests of endothelial cells and increased glial elements. These changes are not appreciated clinically, of course, but are represented by tortuosity and dilatation of the retinal vessels. In the second stage of the disease, the proliferated endothelial cells canalize and break through the internal limiting membrane. With the progression of the disease, there is an increase in the canalization of the endothelial nests. Hemorrhages occur from the newly formed vessels, and then organized contraction and folding of the retina begin. Masses of angiomatous tissue creep between the retina and the hyaloid membrane of the vitreous and then invade the vitreous proper. Ultimately, the greater part of the retina becomes involved and is folded and detached as a result of contraction. Secondary complications, such as glaucoma, follow.

It is noteworthy that the area of the ora serrata was not involved in any of the cases. The internal limiting membrane appeared normal throughout. There was no evidence to indicate that an inflammatory process or congenital nonattachment of the retina played a role in the causation of retrolental fibroplasia.

Autopsies in these 10 cases revealed no changes in the viscera which could be correlated with retrolental fibroplasia. A twin of one of the stillborn infants in this series of premature births subsequently had retrolental fibroplasia. The birth weight of the twin who died four hours after birth was 1,200 gm. No changes indicative of early retrolental fibroplasia were found in the eyes.

The second half of this report is devoted to a study of 194 eyes from 97 newborn or stillborn premature infants whose birth weight ranged from 200 to 2,500 gm. The purpose of this part of the investigation was to determine whether or not subclinical histological changes of retrolental fibroplasia which cannot be observed with the ophthalmoscope were present in the periphery of the fundus of normal premature infants. In only four eyes (two cases) could pathological changes identical with those described in early retrolental fibroplasia be found. One of these cases, that of a stillborn infant with a birth weight of 1,950 gm., has been previously reported. In the second case death occurred 48 hours after birth. The weight was unknown. In this case the characteristic thickening of the retina and nests of endothelial cells with beginning canalization were observed. In the left eye a few vessels had broken through the internal limiting membrane into the vitreous.

It was also noted in this histological study that choroidal and retinal hyperemia were more closely correlated with the degree of postmortem autolysis than with the birth weight of the infant. It was therefore concluded that hyperemia of the retina and/or uvea was not a prodromal manifestation of retrolental fibroplasia. Likewise, the absence of the internal limiting membrane of the retina was found to be more closely correlated with postmortem autolysis than with the birth weight. Retinal hemorrhages were found in 25% of the eyes of infants with a birth weight of more than 300 gm. No hemorrhages were found in the eyes of infants weighing less than this at birth. Cells in the uvea which had previously been interpreted as inflammatory,[7] were identified on closer scrutiny as extramedullary hemopoiesis.

In summary, these authors conclude that the earliest basic change in retrolental fibroplasia is an endothelial and glial proliferation, together with a neovascularization in the nerve fiber layer of the retina, which manifests itself first in the equatorial region.

In contrast to their previous opinion that the matrix of retrolental fibroplasia is usually present at birth, the authors now state that such changes can occur, but that this is the exception rather than the rule. Since the new-formed vessels are attracted into the vitreous, they still think that the site of positive taxis is the vitreous. They draw an analogy between the normally avascular cornea and the vitreous in that in a primary disease of the cornea endothelial proliferation and capillary budding occur at the limbus, but the disease in the cornea is the site of taxis for these vessels.

Bembridge [8] reports the examination of two eyes of a baby who weighed 1 lb. 9 oz. (794 gm.) at birth and who died at the age of 3 months. No mention is made of ophthalmoscopic examination of this infant prior to death. On histological examination, endothelial and glial proliferation in the nerve fiber layer and ganglion cell layer and newly formed capillaries in the retina were observed. No vascular abnormalities were noted elsewhere in the body.

Histological examination of eyes with advanced retrolental fibroplasia were made by a number of other workers.[9]

7. Reese, A. B., and Blodi, F. C.: Retrolental Fibroplasia: Fifth Francis I. Proctor Lecture, Am. J. Ophth. **34**:1, 1951.

8. Bembridge, B. A.: A Study of Cases of Retrolental Fibroplasia Seen in Oxford, Tr. Ophth. Soc. U. Kingdom **71**:605, 1951.

9. (*a*) von Winning.[3] (*b*) Bembridge, B. A.; Coxon, M.; Holton, A. C. L.; Jackson, C. R. S., and Smallpiece, V.: Retrolental Fibroplasia: A Problem of Prematurity, Brit. M. J. **1**:675, 1952. (*c*) Jefferson, E.: Retrolental Fibroplasia, Arch. Dis. Childhood **27**:329, 1952.

Incidence and Clinical Course.—The actual incidence of retrolental fibroplasia in the United States is not known. Wide and unexplained variations in incidence among institutions in the same geographic area and among different geographic areas continue to be reported. The disease is found most constantly in premature infants weighing less than 3 lb. (1,307 gm.) at birth. Fifty to 60% of this group have early manifestations of the disease, and 10 to 20% have permanent residual lesions. Occasional cases of the disease occur in infants of more than 4 lb. (1,814 gm.) birth weight. It has been pointed out that a compilation of the geographic incidence of retrolental fibroplasia would be of great value in the study of this disease and that these data could best be collected by an organization such as the National Society for the Prevention of Blindness.[4]

Early reports indicated that retrolental fibroplasia was confined primarily to the United States. However, during the past few years reports have appeared from other countries, and the incidence in many countries is apparently comparable to that found in the United States.[10]

At a pediatric research conference on retrolental fibroplasia,[4] it was pointed out that there is a definite need for standardization of classification and description of the stages of retrolental fibroplasia. This would aid in evaluating the reports on the incidence and methods of treatment of this condition.

Several authors [11] list the differences in the ophthalmoscopic appearance of the normal fundus in infants and in adults. In infants the optic disk is relatively pale or grayish, and the physiological cup is either absent or extremely small. The foveal reflex is absent, and the whole macular area has a "mother-of-pearl" appearance, which is particularly striking in Negro infants. About two-thirds of the infants have a yellowish or grayish-white reflex in the far periphery of the fundus. The absence of a sharply defined choroidal pattern and the spherical aberrations in the periphery of the cornea and lens make it difficult to decide whether or not this grayish portion of the fundus is slightly elevated. These normal variations in the fundus of the premature infant are very difficult to distinguish from moderately advanced retrolental fibroplasia and may confuse the inexperienced observer in early cases of the disease.

Two classifications of the various stages of retrolental fibroplasia have been given. Owens and Owens [11b] divide the process into four stages.

Stage 1: Vascular changes. These extend from the earliest detectible abnormality, which is usually a slight dilatation of the retinal arteries and veins, to marked dilatation and tortuosity in which the retinal vessels turn in sharp, hairpin curves to reverse on themselves, and then turn again to run toward the periphery.

10. (*a*) von Winning.[3] (*b*) Crosse, V. M., and Evans, P. J.: Prevention of Retrolental Fibroplasia, A. M. A. Arch. Ophth. **48**:83, 1952. (*c*) Brown, C. A., and Corner, B.: Retrolental Fibroplasia: Early Development and Effect of ACTH in Treatment, Brit. J. Ophth. **36**:281, 1952. (*d*) Ryan, H.: Retrolental Fibroplasia, Tr. Ophth. Soc. Australia **11**:122, 1951. (*e*) Jefferson.[9e] (*f*) Coxon, M. W.: A Study of Cases of Retrolental Fibroplasia Seen in Oxford, Tr. Ophth. Soc. U. Kingdom **71**:591, 1951. (*g*) Crosse, V. M.: Problem of Retrolental Fibroplasia in the City of Birmingham, ibid. **71**:609, 1951. (h) Huggert, A.: Appearance of the fundus Oculi in Premature Infants, with Special Reference to the Early Stages of Retrolental Fibroplasia, Acta pædiat. **41**:453, 1952.

11. (*a*) Huggert.[10h] (*b*) Owens, W. C., and Owens, E. U.: Retrolental Fibroplasia, Tr. Pennsylvania Acad. Ophth. & Otol. **5**:139, 1952.

Stage 2: Localized or generalized infiltration of the retina. This develops shortly after the appearance of the vascular changes and consists of localized or generalized grayish-yellow areas. Frequently the infiltrations begin in the periphery of the fundus, but at times they may appear also in the posterior pole. Numerous small hemorrhages appear on the surface of the retina in the areas of localized infiltration. Rarely are the hemorrhages large or extensive. If the retinal changes are generalized, the entire fundus becomes grayish-green. The vessels are obscured, and the margins of the disk become blurred by the development of a generalized retinal and vitreous haze.

Stage 3: Retinal separation and the formation of retinal folds. As the disease progresses, the retina becomes detached and appears as a grayish mass with numerous new-formed vessels coursing over it. These folds occur first in the periphery of the fundus, and at this stage the vitreous becomes extremely hazy. At first the detachments may be localized to one area of the fundus, but eventually the entire retina becomes detached.

Stage 4: Complete retrolental membrane. A complete retrolental membrane is formed by the gradual fusion of the peripheral folds of the detached retina with the tissue formed by the proliferative retinitis. Broad ciliary processes may be seen extending into the membrane at its periphery. Occasionally small hemorrhages occur into the membrane. At this stage of the disease the cornea stops growing, and the eye appears microphthalmic. The anterior chamber becomes progressively shallower; a posterior synechia forms, and the eye develops a gray, atrophic appearance.

Reese and his co-workers [12] divide both the acute and the cicatricial phase of the disease into various stages. In the acute phase they list five subgroups, or stages: Stage 1 is characterized by tortuosity of the retinal vessels plus neovascularization. During this stage vascular dilatation is usually present, but not necessarily so. Hemorrhages may or may not be noted. Tortuosity and neovascularization are usually seen in the extreme periphery of the visible fundus. Stage 2 includes Stage 1 plus some peripheral edema and vascular dilatation. Hemorrhages are usually present. Spontaneous regression may occur. Stage 3 includes Stage 2 plus a large amount of edema and retinal detachment in the periphery of the visible fundus. Spontaneous regression at this point is unlikely. Stage 4 is characterized by a hemispherical or circumferential retinal detachment. At this time a large area of the retina is usually elevated, but some retina still remains in position. Stage 5 is complete retinal detachment.

For greater ease in recording data and for discussion of the end-results of therapy, five grades of the cicatricial phase are also described. Grade 1 is characterized by a pale appearance of the fundus with attenuated blood vessels. Grade 2 includes Grade 1 plus small masses of opaque tissue in the periphery with or without visible retinal detachment. The disk is distorted by traction and displacement of the retina toward the sides of the tissue mass, which is usually located temporally. If the process ends at Grade 1 or Grade 2, the patient usually has useful vision. In Grade 3 there are large masses of opaque tissue in the periphery, and these masses incorporate a retinal fold, which extends to the disk. Visual acuity with this degree

12. Reese, A. B.; Blodi, F. C.; Locke, J. C.; Silverman, W. A., and Day, R. L.: Results of the Use of Corticotropin (ACTH) in the Treatment of Retrolental Fibroplasia, A. M. A. Arch. Ophth. **47**:551, 1952.

of damage usually varies from 5/200 to 20/50. In Grade 4 retrolental tissue covers part of the pupillary area. A small area of retinal detachment may be visible, or only a red reflex over a sector of the fundus is seen. In Grade 5 retrolental tissue covers the entire pupillary area and no fundus reflex can be obtained. Grades 4 and 5 result in blindness.

Etiology.—A number of interesting papers have appeared during the past year which suggest that a defect in the oxygen metabolism of the retina in the premature infant is the cause of retrolental fibroplasia. It has been pointed out that the retina of an infant weighing about 3 lb. at birth is not completely vascularized. It is suggested that during the first few months of extrauterine life pediatric management so disturbs the oxygen metabolism of the retina that in some instances hemorrhages and vascular proliferation occur, with resulting retinitis proliferans and detachment. It is interesting that there are clinical statistics which support both the theory that this disturbance is caused by hyperoxia (oxygen poisoning) and the theory that it is due to anoxia.

Patz, Hoeck, and de la Cruz [13] offer evidence to support the theory that high-oxygen therapy is the cause of retrolental fibroplasia. They point out that studies on the fetus in utero shows that the oxygen saturation of arterial blood is approximately 50%. Within a few hours after birth the oxygen saturation of arterial blood rises to approximately 90% at room atmosphere (20% oxygen). When an infant is placed in an atmosphere containing 30 to 50% oxygen, the arterial oxygen saturation rises to 92 or 93%. When the infant is placed in a 30 to 55% oxygen concentration, the arterial saturation rises to 96%, and when it is placed in a 70 to 79% oxygen concentration, 100% arterial saturations have been recorded. The authors also point out that the toxic effects of hyperoxia in man and animals is well established. Animals placed in 80% oxygen typically show oxygen poisoning with acute pulmonary edema, which develops in three to eight days. Young rats, rabbits, and mice have been reported to be relatively immune to sustained high oxygen levels, but young puppies are very susceptible, as much so as adult dogs. On the basis of these observations, the authors reason that the final maturation of the premature infant in an incubator with a high oxygen saturation, in contrast to the final development in utero at low oxygen tensions, may result in an abnormal proliferation of the retinal vessels.

They attempt to evaluate the possible role of oxygen therapy in retrolental fibroplasia on the basis of a study of infants at the Gallinger Municipal Hospital from January, 1948, to January, 1951. Infants with a birth weight of 3.5 lb. (1,534 gm.) or less were placed in one of two groups on admission to the premature nursery. Group 1 was maintained on a high oxygen saturation (65 to 70%) for four to seven weeks; Group 2 received lower oxygen (under 40%) concentrations. The nursery routine was otherwise identical in the two groups.

Infants were placed in high or low oxygen concentrations on an alternate admission basis regardless of birth weight. Oxygen tensions were controlled by incubator samplings taken at eight-hour intervals with an electronic analyzer (accurate within 2% concentration). The infants were gradually weaned from the high oxygen level by gradually reducing incubator concentrations over a one-week period. Weaning

13. Patz, A.; Hoeck, L. E., and de la Cruz, E.: Oxygen Administration in Retrolental Fibroplasia, Am. J. Ophth. **35**:1248, 1952.

from the low oxygen level was done over one to three days. The infants in each group were examined ophthalmoscopically at regular intervals and followed after discharge in a special clinic until they were 6 months of age. Table 1 shows the results of a study of 65 infants.

While the study of Patz and co-workers was in progress, Szewczyk [14] reported that when infants were removed from high oxygen levels to room atmosphere, the retinal vessels dilated and hemorrhage and edema of the retina appeared within a few days. When the babies were returned to high oxygen concentrations, uniform regression of the disease was noted. The authors attempted to confirm Szewczyk's observations by removing two infants from a concentration of 70% oxygen to room atmosphere (approximately 20% oxygen). Both babies weighed less than 3 lb. at birth and had been in 70% oxygen for 32 days. On examination immediately prior to removal from the incubator, dilatation and tortuosity of the retinal vessels, vitreous haze, and an index myopia of approximately 6 D. were noted in each infant. In addition to these findings, Baby B had localized areas of retinal edema along the vessels. Infant A required supplements of oxygen for one and one-half hours after feedings for the first 48 hours. Infant B required supplementary oxygen on two occasions after feeding.

TABLE 1.—*Results of Study of Sixty-Five Infants*

Oxygen Level	Total No. of Infants	Normal Eyegrounds	Retrolental Fibroplasia				
			Grade				
			1	2	3	4	Total
High	28	11	3	7	2	5	17 (60%)
Low	37	31	4	2	0	0	6 (11%)

The eyes of these two infants were examined daily for 4 days, then at 2-day intervals until the 10th day, and then once a week for 60 days. Infant A showed no change in the eyegrounds for the first four days at room oxygen. Subsequently, the retrolental fibroplasia regressed, the vitreous cleared, and the dilated vessels returned to normal. Infant B showed a slight, but definite, increase in the caliber and tortuosity of the arteries and veins during the first four days out of high oxygen concentration. A solitary hemorrhage appeared in the nasal periphery of the left eye on the third day. This hemorrhage cleared, and 21 days after the infant's removal from the incubator the retinal vessels had gradually resumed normal size. The eyes of both infants had remained normal to the time of the report, at the age of 3 months.

Patz and his co-workers state that this evidence strongly suggests that high oxygen administration is a factor in the pathogenesis of retrolental fibroplasia. However, in view of the bizarre manner in which the incidence of the disease fluctuates, additional rigidly controlled observations are necessary to establish this concept. The authors also suggest that a prolonged high oxygen concentration may be injurious as a result of its direct effect, rather than because of the relative anoxia that may follow too rapid removal from oxygen, as cited by Szewczyk.[14]

14. Szewczyk, T. S.: Retrolental Fibroplasia: Etiology and Prophylaxis, Am. J. Ophth. **35**:301, 1952.

Ryan [15] favors the theory that the use of high concentrations of oxygen influences the development of retrolental fibroplasia. He states that prior to 1948 no case of this disease occurred in the Woman's Hospital in Melbourne, Australia. From 1948 to 1951 the most efficient oxygen cot available was used. During this time the incidence of retrolental fibroplasia in a series of 124 babies weighing under 3 lb. at birth was approximately 17%. The exact concentration of oxygen used and the length of time that the infants were kept in oxygen during this period are not known, but the author believes the babies were kept for a week or more at a concentration of 40 to 60%. During the first nine months of 1951 the hospital staff returned to the policy of administering oxygen only when the babies were cyanotic, and not one case of retrolental fibroplasia occurred.

Bousquet and Laupus [16] examined the fundi of 107 premature infants with a birth weight of less than 1,650 gm. who had been placed in either the Gordon-Armstrong or the Isolet type of incubator under high oxygen concentrations until a weight of 1,500 gm. had been reached. Seventeen of these infants showed an increase in venous caliber and arterial tortuosity of the retina before removal from the incubator. In addition, 3 of the 17 infants exhibited preretinal vitreous hemorrhages.

Goldman and Tobler [17] think that high oxygen concentrations contribute to the development of retrolental fibroplasia. Prior to 1945, a total of 570 premature babies with a birth weight of less than 4 lb. had been delivered in the Infants' Home in Berne, Switzerland. In none of these infants did retrolental fibroplasia develop. In 1945 use of high oxygen concentrations, up to 60%, was introduced, and retrolental fibroplasia developed in two infants.

Szewcyzk [14] is one of the staunchest advocates of the belief that retrolental fibroplasia is a result of anoxia. He states:

> Retrolental fibroplasia is a terminal stage of uncompensated anoxic retinopathy in prematures, and . . . it is directly related to oxygen environment of prematures.

In support of this statement, he points out that normal adults cannot withstand a sudden transfer to lowered oxygen concentrations without showing signs of disturbance of the central nervous system, and that the severity of these manifestations is proportional to the decrease in oxygen tension. Moreover, it takes several days for a normal adult to become accustomed to an atmosphere of decreased oxygen pressure. He thinks, therefore, that it is unreasonable to assume that an infant can tolerate a sudden change in oxygen environment from a concentration of 80 or 90% to one of 20%.

In the Christian Welfare Hospital of East St. Louis, 347 premature infants were admitted and treated during 1950. In eight of these infants severe retrolental fibroplasia developed. In the last 10 months of 1951, a total of 263 premature infants were admitted, and 20 of these had the disease, with partial or complete loss of vision. In every case the retrolental fibroplasia developed shortly after the child was removed from the incubator.

15. Ryan, H.: Retrolental Fibroplasia: A Clinicopathologic Study, Am. J. Ophth. **35**:329, 1952.

16. Bousquet, F. P., Jr., and Laupus, W. E.: Studies on the Pathogenesis of Retrolental Fibroplasia, Am. J. Ophth. **35**: (no. 5, Pt. 2)64, 1952.

17. Goldman, H., and Tobler, W.: Etiology of Retrolental Fibroplasia, Schweiz. med. Wchnschr. **82**:381, 1952.

As a result of these observations, the author attempted to discover whether or not retrolental fibroplasia was the result of retinal anoxia by performing two experiments. In the first, he treated nine infants with early retrolental fibroplasia by placing them in oxygen incubators. All had marked vascular tortuosity and neovascularization; eight had pronounced vascular engorgement; five had retinal hemorrhages, and four had definite retinal elevation. In all cases the disease was immediately arrested when the patients were placed in the incubator. A further follow-up study of these infants revealed that five have been discharged from observation: Three of these have normal fundi; one has tortuous and new-formed vessels in the retina, and the fifth shows some white peripheral patches in an otherwise normal fundi. The four remaining patients had a relapse after return to the incubator because the oxygen concentration in the incubators was not kept at a steady level. One of these infants has pronounced bilateral retinal detachments; a second has a peripheral retinal detachment in one eye and pronounced pigmentary degeneration in the other; a third has one normal eye and a flat temporal detachment in the other; the fourth has a small peripheral retinal fold in one eye and a white, atrophic patch in the extreme temporal periphery of the other.

In a second experiment, 19 premature infants whose general condition made it safe were removed from the incubator. Eight who were removed from oxygen administered at a rate of 4 liters per minute (concentration unknown, but probably high) were placed in a nursery where the oxygen concentration was between 22 and 25%. Eleven infants had their oxygen concentration gradually reduced to about 40% and were then placed in the nursery. None of these children had difficulty in breathing or change in color or disposition. Within 24 to 48 hours all infants showed dilatation of the retinal vessels. In 12 infants peripheral neovascularization developed within one to four days. Eight infants manifested retinal hemorrhages in 1 to 10 days, and 16, edema of the peripheral retina in 1 to 8 days. It was necessary to return nine of the babies to the incubator with high oxygen concentrations because of alarming progression of retinal changes. Without exception, all the babies returned to the incubator showed marked improvement within 24 hours, and within three to four days the fundi were almost normal in appearance. Ten of the infants who showed retinal changes after withdrawal from oxygen returned to normal without further oxygen therapy.

On the basis of this study, the author thinks that premature babies who weigh over 4 lb. and who show no signs of anoxia should not be placed in oxygen. The fundi, however, should be carefully watched, and if signs of progressive anoxic retinopathy develop, the infant should be placed in an incubator and given an oxygen concentration of 40 to 45%. Premature babies weighing under 4 lb. at birth should be placed in an oxygen atmosphere of 45% and weaned off slowly. The optimal concentration of oxygen or the time the child should be kept in the incubator is still unknown.

These studies of Szewczyk have stimulated a great deal of interest in the influence of oxygen on the development of retrolental fibroplasia. However, they lack one very important criterion, which should be included in any study of the disease; that is an alternate or a random selection of cases.

Crosse and Evans [10b] also think that retrolental fibroplasia is caused by the increased use of high concentrations of oxygen early in the life of the premature

infant. In support of this theory, they point out that in Birmingham, England, the incidence of retrolental fibroplasia was extremely low before 1949, but that it increased to a striking degree between 1949 and 1950. The only change in the treatment of the premature infants which showed any significant relation to the incidence of the disease was the amount and duration of oxygen administered. From July, 1950, to July, 1951, when the administration of oxygen was reduced to a minimum, the incidence of the disease again dropped (Table 2).

It is the opinion of the authors that retrolental fibroplasia is not due to the administration of insufficient oxygen, for if so, it would then be impossible to explain the almost total absence of the disease prior to 1949, when little use was made of oxygen. Nor is it due to oxygen poisoning, for the disease is not observed in infants while they are still under oxygenation. Crosse and Evans state that more probably the changes in the retina result from a primary adjustment of the retina to high oxygen tension, whereby the retina loses its ability to accommodate itself to relative anoxia on the infant's removal to atmospheric oxygen, having acquired an inertia of response.

TABLE 2.—*Effect on Survival Rates and Incidence of Retrolental Fibroplasia of Oxygen Administration to Premature Infants in Unit A*

Period *	Birth Weight 2.3 Lb. (907-1,307 Gm.)	Survivors (6 Mo.)		Retrolental Fibroplasia	
		No.	Per Cent	No. of Infants	Per Cent of Survivors
A 1931-1945	339	105	31.0	0	0
B 1946-1948	73	27	37.0	1	3.7
C 1949-June 1950	69	26	37.7	5	19.2
D July, 1950-1951	54	24	44.5	0	0

* In Periods A and B there was little use of oxygen; in Period C, much use of oxygen, and in Period D, a return to minimal use of oxygen.

Jefferson [9c] states that of 629 infants who were born in Manchester, England, before 1950, retrolental fibroplasia occurred in only 3. Eighty-two of these infants weighed less than 3½ lb. at birth. In 1950 to 1951, the author observed 53 infants with retrolental fibroplasia. The incidence for 72 babies weighing under 3½ lb. at birth was 43%. (It is difficult to determine from these statistics whether these 53 infants had early retrolental fibroplasia or impairment of vision. It is mentioned that at least 28 of them had leucocoria.)

Before 1949, in Manchester premature babies were given oxygen by face mask as a routine and only rarely were placed in oxygen tents. In December, 1949, oxygen tents were installed and used routinely for all infants with a birth weight of less than 3 lb. In November, 1950, it was decided to nurse every infant naked in oxygen tents. After this, in babies whose birth weight was over 3 lb. the disease began to appear. In October, 1951, the use of oxygen was reduced to a minimum, and its withdrawal was carefully graded. In the 16 infants weighing under 4 lb. at birth who have been observed since October, 1951, only one serious case and two mild cases of retrolental fibroplasia have developed.

In six cases the early changes of the disease were noted to regress rapidly when the infants were replaced in high oxygen concentrations. These observations led the author to conclude (1) that variations in the method of administration of oxygen

appear to be closely linked with the incidence of retrolental fibroplasia, and (2) that retrolental fibroplasia may develop when the tension of oxygen available to the tissues of the premature infant is suddenly lowered

Von Winning [3] observed in the Netherlands a correlation between the use of high concentrations of oxygen and the incidence of retrolental fibroplasia. He also noted a regression of early lesions of the disease when the child was replaced in high oxygen concentrations.

Rubinstein [18] suggests that there are three reasons that a premature birth may produce anoxia and the accumulation of metabolites, with resultant development of vasodilatation of the retinal vessels and exuberant budding of the terminal capillaries. 1. The hyaloid system of vessels closes precociously. 2. Physiological anemia of the premature baby and lowering of the oxygen carried in the blood aggravate the local anoxia. 3. Exposure to light and the establishment of pupillary reactions put additional metabolic stress on the ciliary region.

Two experimental studies on animals reported during the past year have given support to the theory that the development of retinal vessels in the premature infant may be related to the administration of oxygen or anoxia. Ingalls and his co-workers [19] studied the influence of anoxia on pregnant mice; 510 animals were used in the experiment and were divided into three equal groups. In Group A the animals were exposed for five hours to the atmospheric equivalent of an altitude of approximately 27,000 ft. (9,000 meters); in Group B they were exposed to negative pressures comparable to that at an altitude of 25,000 ft. (8,370 meters), and Group C were used as controls. The 170 animals in each of the experimental groups A and B were divided into 17 subgroups, with 10 animals each. Members of each subgroup, in succession from the 1st to the 17th day of pregnancy, received the anoxic insult on one occasion only. The contents of the uterus were delivered by surgical section on the 18th day of gestation. (The normal gestation period of mice is 22 days.)

A condition known as "open eye" occurred in 10 animals; in 4 animals of Group A, in 4 animals of Group B, and in 2 animals in the control group (Group C). The two animals with "open eye" in the control group were litter-mates. The ocular abnormality occurred only when the anoxic insult was given after a gestation of 16 $\pm$1.5 days.

Normally mice are born with their eyelids closed, and they do not open their eyes until the 12th or 14th day after birth. In the condition known as "open eye" the palpebral fissures are open; the capsule of the lens is ruptured; remnants of the retrolental portion of the hyaloid artery are present, and the vitreous is filled with blood channels and an embryonic type of connective tissue. The retina is detached and thrown into folds behind the lens material. The pathological description of the retinal changes in this condition do not sound a great deal like retrolental fibroplasia. This condition may occur as a genetic defect, or it may result from injury to female mice at the appropriate time during gestation by exposure to x-rays or use of vitamin-deficient diets.

18. Rubinstein, K.: Mechanism of Retrolental Fibroplasia, Brit. J. Ophth. **36**:303, 1952.

19. Ingalls, I. H.; Tedeschi, C. G., and Helpern, M. M.: Congenital Malformations of the Eye Induced in Mice by Maternal Anoxia, with Particular Reference to the Problem of Retrolental Fibroplasia in Man, Am. J. Ophth. **35**:311, 1952.

Michaelson,[20] in 1948, described and illustrated the retinal vascular development in man and in the cat. He noted that the formation of the capillaries is a function of the veins. Only the arteriae afferentiae appear to originate from arteries. When the vein and the artery are close together, the capillary growth takes place initially from the side of the vein remote from the artery. He also noted that the spread of the capillary growth toward an artery extends only for a certain distance, leaving in the definitive human eye a well-marked capillary-free space around the arteries. These anatomical facts suggest the presence of a factor which affects the growth of retinal blood vessels.

Campbell [21] postulates that the higher oxygen tension which might exist around retinal arteries may inhibit further extension of the venous capillaries during their development and so account for the clearly demarcated capillary-free zone. This hypothesis was tested on rats in which the retinal vessels had just begun to develop from the hyaloid vessels at birth. Ten litters of Wister-strain rats were placed in low pressure chambers with an altitude equivalent of 17,500 ft. (5,835 meters) 24 to 30 hours after birth. Ten other litters were used as controls and were allowed to remain at the normal atmospheric pressure. The pressure was raised at least once a day in gaining entry to the chamber.

At the end of the experiment, the retinal vessels were filled with India ink by injecting the left ventricle under a pressure of 100 mm. Hg until the skin of the head and neck was jet-black. A low-pressure environment produced three changes in the mode of retinal development: 1. The capillaries first formed developed more rapidly toward the definitive type found in the adult rat. 2. The capillary-free zone normally found around the arteries is narrowed. 3. The rate of vascularization of the retina is diminished. The results of this investigation suggest that the oxygen tension in the retina is one of the factors influencing the morphogenesis of the retinal vessels.

The foregoing evidence that retrolental fibroplasia is related either to hyperoxia or to the administration of oxygen and its sudden withdrawal is extremely impressive. There are certain studies, however, that do not conform exactly with these conclusions. First, both Friedenwald [5] and Reese [6] and their co-workers, on postmortem examination of infants who had typical retrolental fibroplasia, failed to detect any vascular abnormalities in organs other than the eye which were caused by hyperoxia or anoxia. Second, Silverman and his co-workers,[22] in their excellently documented report, tabulated the age at which oxygen administration was discontinued and the age at which the clinical onset of the disease was noted in 80 infants with retrolental fibroplasia. The fundi of all the babies were examined at least once a week. In 11 infants the disease was discovered while they were under continuous oxygen administration; for 15 infants, 1 to 7 days elapsed between the cessation of oxygen administration and the onset of retrolental fibroplasia; for 17 infants, 8 to 14 days; for 13 infants, 15 to 21 days, and for 13 infants, more than

20. Michaelson, I. C.: Mode of Development of the Vascular System of the Retina, with Some Observations on Its Significance for Certain Retinal Diseases, Tr. Ophth. Soc. U. Kingdom **68**:137, 1948.

21. Campbell, F. W.: Influence of a Low Atmospheric Pressure on the Development of the Retinal Vessels in the Rat, Tr. Ophth. Soc. U. Kingdom **71**:287, 1951.

22. Silverman, W. A.; Blodi, F. C.; Locke, J. E.; Day, R. L., and Reese, A. B.: Incidence of Retrolental Fibroplasia in a New York Nursery, A. M. A. Arch. Ophth. **48**:698, 1952.

3 weeks. It would seem that if either the administration of oxygen or its withdrawal had been the cause of retrolental fibroplasia, there should have been a closer correlation between the use of oxygen and the onset of the disease.

Likewise, Houlton [23] reports that because the use of high oxygen concentrations had been correlated with the rise in the incidence of retrolental fibroplasia, oxygen concentrations at Oxford, England, were lowered. Cases continued to appear, however, even after the reduction in the use of oxygen.

When these various observations are reviewed, it seems likely that the administration of oxygen to the premature infant does play a part in the development of retrolental fibroplasia. It is well established that vascular dilatation and congestion of the retinal vessels occur when a child is taken from a high oxygen tension, of approximately 70%, to an atmospheric oxygen pressure, of 20 to 25%. This change may not be enough in itself to produce the typical picture of retrolental fibroplasia, but it may well be the final factor that is necessary to produce abnormal vascular proliferation in a retina which is struggling to maintain its normal metabolism. Likewise, the prolonged administration of high concentrations of oxygen (oxygen poisoning), as suggested by Patz and his co-workers [13] and by Crosse and Evans,[10b] could be a detrimental factor in the development of the premature retina.

It is unlikely, however, that administration of oxygen will be the sole solution to this complex problem, for not all infants with a birth weight of under 3 lb. who have been kept in high oxygen concentrations and removed suddenly from this environment show signs of retinal disease, nor does every patient with early manifestations of the disease show a dramatic response on return to high oxygen concentration. Likewise, oxygen poisoning cannot always be a factor, for I have seen at least two infants with moderately advanced retrolental fibroplasia who weighed over 7 lb. (3,175 gm.) at birth and received no supplemental oxygen.

Silverman and his co-workers [22] have made a number of interesting observations on premature infants with retrolental fibroplasia. Their report is based on patients admitted to Babies Hospital, in New York, between Dec. 15, 1949, and Dec. 15, 1951. Of 437 infants admitted to the nursery, 140 died within 7 days, and 17 between 7 and 84 days, after admission. Five of these 17 infants had retrolental fibroplasia which was recognized clinically before death. Of the 280 infants who were discharged from the nursery alive, 75 had retrolental fibroplasia, and 19 of this group were left with serious involvement of one or both eyes.

The authors found that the incidence of hemangioma of the skin was inversely related to the birth weight, but that these lesions did not occur in a higher percentage of infants who had retrolental fibroplasia than in infants of a similar birth weight who did not have the ocular disease. Likewise, there was no correlation between the ocular changes and the incidence of other congenital abnormalities in 80 infants in whom retrolental fibroplasia developed. A positive correlation was found between the incidence of the disease and a low birth weight. There was no difference in the correlation between birth weight and gestational age. Interestingly, an inverse relationship was shown between the birth weight and the age at which the first vascular signs of retrolental fibroplasia were noted. The heavier infants had manifestations sooner after birth than did the smaller ones. However, the age of onset

23. Houlton, A. C. L.: Study of Cases of Retrolental Fibroplasia Seen in Oxford, Tr. Ophth. Soc. U. Kingdom **71**:583, 1951.

of the lesion did not coincide with the expected day of delivery. Except for a single instance, the disease manifested itself before the expected date of birth at full term. The severity of the disease was unrelated to the degree of prematurity.

Hepner and Krause[24] attempted to correlate the relation of the incidence of retrolental fibroplasia to the feeding of premature infants on a "high-electrolyte diet" and to repeated blood transfusions. They noted that a 1,650-gm. infant taking 150 cc. per kilogram of body weight a day of undiluted half-skimmed cow's milk with 10% added carbohydrate had a sodium intake of 6.05 mEq. a day. A similar infant taking the same amount of a similar formula to which was added carbohydrate containing 2% sodium chloride had a sodium intake of 14.0 mEq. a day. On human milk the sodium intake of a similar infant would be 1.6 mEq. a day.

In order that the authors might test the influence of a high- and low-electrolyte diet on the development of retrolental fibroplasia, 24 infants weighing from 850 to 1,540 gm. at birth were divided into two equal groups. One group was treated differently from the other only in the kind of food offered. The first group was fed nothing but water and ordinary human milk until a weight of 1,800 gm. was obtained and then was isocalorically transferred gradually over a week's time to the formula fed the second group. The second group was fed autoclaved cow's milk with half the cream removed and 10% carbohydrate added. In 3 of each group of 12 infants retrolental fibroplasia developed. No patient receiving human milk had even the first change of retrolental fibroplasia before being transferred to formula feeding. (In view of the observations of Silverman and his co-workers, it would be interesting to know the birth-weight distribution in the two groups and the time at which the infants fed a "high-electrolyte diet" had onset of retrolental fibroplasia.) It was noted that during and immediately after the transfer of the 12 infants from human to cow's milk, there was a sharp increase in weight gain, followed by resumption of normal weight gain. This observation was consistent in all 12 infants, although there was a variation in the degree of change. At the time of the sharp increase in weight, the general appearance of the infant changed. Contours of the infants were rounded by mild thickening and hardening of the skin, reminding one of the sleek appearance of infants with mild scleroderma. In three infants this process advanced until frank pitting of the scalp and ankles could be demonstrated. Two of these infants were returned isocalorically to feeding with human milk. Diuresis and loss of weight, with disappearance of edema, ensued.

The authors also commented that blood transfusion for prophylaxis of anemia of prematurity has been an increasingly common practice during the past few years and that this trend may have a bearing on the etiology of retrolental fibroplasia. To discover whether blood transfusions might have any effect on the disease, the records of 20 infants born weighing less than 1,500 gm. were reviewed. Eight of these infants had retrolental fibroplasia, and 12 did not. Every infant with retrolental fibroplasia had received a transfusion. The average number of transfusions for infants with the disease was 3.3 per infant, and the average amount of transfusion was 12 cc. per kilogram of body weight. In normal infants the average number of transfusions given was 2.0 per infant, and the average volume of the transfusion per kilogram was 4.6 cc.

24. Hepner, W. R., Jr., and Krause, A. C.: Retrolental Fibroplasia: Clinical Observations, Pediatrics **10**:433, 1952.

After these observations were made, ophthalmoscopic examinations were routinely done before and after the transfusion in four infants with early retrolental fibroplasia. Either retinal detachment or severe intraocular bleeding was seen to follow transfusion in these four infants.

The influence of the electrolyte intake on retrolental fibroplasia was further studied by reviewing the incidence of permanent blindness due to retrolental fibroplasia at the Chicago Lying-In Hospital in relation to the type of feeding of infants born weighing less than 1,501 gm. Between 1937 and 1946, there were 84 infants of this birth weight who survived. A "low-electrolyte" diet was given during this time, and the incidence of the disease was 7%. From 1946 to 1949 a high-electrolyte diet was given. Of 49 infants observed in this group, 45% had the disease. In 1950 and in the first six months of 1951, a low-electrolyte diet was again instituted, and of 19 infants weighing less than 1,501 gm. none had retrolental fibroplasia.

The authors conclude that two factors, a formula of high-electrolyte concentration and blood transfusions, may overload the capacity for physiological adjustment of small premature infants and lead to retrolental fibroplasia.

Hepner and Krause [24] attempted to produce retrolental fibroplasia in kittens by disturbing their fluid and electrolyte balance. (It should be recalled that Michaelson [20] demonstrated that the retina of the kitten is not completely vascularized until approximately the 22d day after birth.) Twelve litters of kittens were used. Beginning on the second day of life, half of each litter of newborn kittens was given intraperitoneal infusions of 0.9% sodium chloride, equal to 10% of the body weight. Vasopressin (Pitressin) tannate in oil, 0.2 to 0.5 cc., was given twice a week. When edema of the paws and lids was established, massive transfusions of the mother's blood were given intravenously until gasping and cyanosis were evident. These transfusions were repeated twice a week for periods ranging from 13 to 43 days.

On histological examination of the eyes, the treated group was found to differ from the controls in that there was persistence of the hyaloid system and pupillary membrane in the treated animals. The retinal vessels were dilated, and midway between the ora serrata and the optic nerve several angiomatous clumps of vessels were seen in the retina. These vessels did not enter the vitreous. The retinal lesions in these experiments resembled to some degree those described in early retrolental fibroplasia. However, the general picture differs from that in the human eye in that there is a persistence of the hyaloid system in the kitten.

One obvious difference in infants who mature in utero and those born prematurely is that the eyes of the premature infants are exposed to light at an earlier age. It is known that a complex biochemical reaction occurs when the light strikes the retina and metabolism of the tissue is altered. It is not inconceivable that such change in the chemical environment of the developing capillaries may act as a stimulus to their abnormal growth. Locke and Reese [25] performed experiments on premature infants to determine whether exposure of the eyes to light or the action of mydriatic drops had any influence on the development of retrolental fibroplasia. Accordingly, one eye of each of 22 babies whose birth weight was 2,000 gm. or

25. Locke, J. C., and Reese, A. B.: Retrolental Fibroplasia: The Negative Role of Light, Mydriatics, and Ophthalmoscopic Examination in Its Etiology, A. M. A. Arch. Ophth. **48**:44, 1952.

less was covered with a firm gauze and adhesive patch in a manner that would shut out light. This was done as soon as possible after birth, and only infants whose eyes were patched within 24 hours were considered in this study. The patch was not removed until the baby was discharged from the hospital, 22 to 75 days after birth, an average of 46 days. Of the infants so treated, 10 showed manifestations of the acute phase of retrolental fibroplasia in the unpatched eye during monocular occlusion. Subsequent examination of the occluded eye revealed almost identical changes. The monocular-occlusion experiments, therefore, did not give any evidence that the absence of exposure to light of one eye prevented retrolental fibroplasia in that eye or lessened the severity of the disease in that eye in respect to the other.

The factors under investigation could not be completely ruled out until binocular-occlusion experiments had been conducted. This was done by applying firm adhesive and gauze patches as soon as possible after birth to the eyes of 33 premature infants with birth weights of 1,800 gm. or less. At the time of the babies' discharge from the hospital, the patches were removed and the eyes were examined ophthalmoscopically. Manifestations of the acute phase of retrolental fibroplasia were found in 15 of the 33 babies at the time of the first ophthalmoscopic examination. No

TABLE 3.—*Total Results for 1950 and 1951 in Eyes with Retrolental Fibroplasia Reaching Progressive Grade 2*

Group	No. of Eyes	Vision Retained	No Vision	Indeterminate Outcome
Treated	64	41 (64%)	14 (22%)	9 (14%)
Untreated	50	29 (58%)	17 (34%)	4 (8%)
Total no. of eyes	114	70	31	13

additional cases of the disease were found on follow-up examination. Of the 15 infants in whom retrolental fibroplasia developed and who had had binocular occlusion, 9 were followed for three months or longer. Four had a severe form of the disease, whereas of 15 infants who had retrolental fibroplasia without binocular occlusion only 3 were blinded.

The results of these experiments would seem to demonstrate that the instillation of mydriatics, premature exposure of the eyes to light, and handling of premature babies for routine ophthalmoscopic examination are not factors in the production of retrolental fibroplasia.

Treatment.—Oxygen administration in the treatment of retrolental fibroplasia will not be mentioned again, for this has been discussed in the section on etiology.

Reese and his co-workers [12] have extended their observations on the treatment of retrolental fibroplasia with corticotropin (ACTH). Fifteen babies were selected at random [26] from 33 infants in whom retrolental fibroplasia had progressed to Stage 2 (see Reese's classification in previous section).

In Table 3 the end-results in the treated and the nontreated group are compared. From these results the authors conclude that corticotropin has no effect on the course of retrolental fibroplasia.

26. Equal numbers of blue and white marbles of the same size were placed in a box. When a case of retrolental fibroplasia progressed to the stage of early progressive edema (Stage 2), a marble was drawn, and the decision to treat was made by its color.

LaMotte and his co-workers[27] observed the influence of vitamin E and corticotropin or cortisone on the development and progress of retrolental fibroplasia. The results obtained from treatment with vitamin E of 17 infants with the disease were very discouraging. Nine babies became blind in both eyes; three became blind or nearly blind in one eye and had impaired vision in the other; only five had normal or apparently normal vision in one or both eyes. Ten of these patients had the onset of the disease during the prophylactic administration of vitamin E.

The results with corticotropin in 21 infants were hardly more encouraging. Nine of the babies became blind in both eyes; three became blind or nearly blind in one eye and had impaired vision in the other; nine had normal or apparently normal vision in one or both eyes.

Similar results were obtained with corticotropin by Lanman and his co-workers.[28] They treated five premature infants with early retrolental fibroplasia with corticotropin. One patient died during therapy, and the death was possibly related to administration of the substance. In the four remaining infants retrolental membranes developed.

Summary and Comment.—The etiology of retrolental fibroplasia is not known, but certain facts appear to be well established.

1. Retrolental fibroplasia is a disease of prematurity, and the incidence of the disease is highest in babies whose birth weight is 3 lb. or less.

2. The incidence of the disease has increased during the past 10 years far out of proportion to the increased survival rate of infants who weigh less than 3 lb. at birth.

3. The incidence of spontaneous regression of early stages of the disease is high (40 to 60%) when no specific treatment is used.

4. The first lesions which have been observed on histological study of eyes with early retrolental fibroplasia is a proliferation of the endothelium of the retinal blood vessels in the nerve fiber layer. This is followed by hemorrhage and invasion of the vitreous by new-formed vessels from the retina.

5. The first evidence of the disease both in histological and in clinical studies in the vast majority of infants occurs after birth.

These factors indicate that the disease is probably due to some phase in the pediatric management of the child. The numerous surveys which have failed to correlate the use of a single substance or method of treatment of the premature infant indicate that there are probably multiple factors which influence the onset and course of the disease.

Evidence that the administration of oxygen is one of these factors is extremely suggestive.

The degree of hydration and electrolyte balance of the infant may well be another factor.

The absence of any of the usual signs of an inflammatory reaction in the histological examination of early cases of retrolental fibroplasia suggests that the disease is not due to an infectious agent.

27. LaMotte, W. O., Jr.; Tyner, G. S., and Scheie, H. G.: Treatment of Retrolental Fibroplasia with Vitamin E, Corticotropin (ACTH) and Cortisone, A. M. A. Arch. Ophth. **47**:556, 1952.

28. Lanman, J. T.; Guy, L. P., and Dancis, J.: Adrenocorticotropic Hormone in the Therapy of Retrolental Fibroplasia, Pediatrics **9**:27, 1952.

Further studies on the cause and treatment of retrolental fibroplasia would be greatly facilitated if a standard nomenclature for the classification and description of the disease were established by ophthalmologists. It would be of value, moreover, if pediatricians would establish a standard method of tabulation of the management and state of health of the premature infant. The establishment of cooperative groups of hospitals to observe the effects of some factors on the incidence and course of the disease would hasten the accumulation of information.

RETINAL TUMORS

Retinoblastoma.—The comparative value of radium and deep x-rays in the treatment of retinoblastoma is discussed by Stallard.[29] The statistics, observations, and comments in his paper are based on the following six series of patients, in four of which treatment was with radon seeds and radium and in two with deep x-rays: (1) the author's series of 32 patients treated with radon seeds and radium disks (1934 to 1951); (2) Foster Moore's series of 5 patients treated with radon seeds (1929 to 1937); (3) 21 patients treated by other surgeons in Great Britain, Canada, Australia, and the United States; (4) eight patients treated with radium needles at Cristie Hospital and Holt Radium Institute, Manchester, England (1935 to 1949); (5) Reese's series of 53 patients treated with x-rays (1934 to 1949), and (6) Windeyer's series of 11 patients treated with deep x-rays (1941 to 1947).

Of the 32 patients in the author's series, 16 were treated with radon seeds, from 1934 to 1938; 13 with radium disks (1948 to 1951), and 3 with deep x-rays and then radium disks. In 1 infant, radium disks were applied to both eyes, so that the total number of eyes treated by this technique was 33. For all three eyes treated with deep x-rays and radium disks the prognosis was unfavorable, for more than half the retina had been destroyed by the neoplasm, and the remainder was detached. These eyes responded poorly and were enucleated. Two showed no definite evidence of active retinoblastoma cells.

Of the 29 patients treated with radon seeds and radium disks, 24 had some useful vision at the time of the report, and there was no evidence of recurrence in the irradiated eyes. Seven of these 24 patients were still alive, more than five years after irradiation, the period of survival being 17, 13, 15, 14, 13 (two patients), and 5 years. In five patients irradiation was a failure. Two patients retained their irradiated eye with no signs of recurrence—one for 14 years, the other for 12 years. In three patients, the irradiated eye was excised because of complications. Microscopic examinations of serial sections of these eyes showed no clear histological evidence of active retinoblastoma cells.

Three patients who had a neoplasm in their remaining eye successfully treated died of a recurrence in the orbit of the excised eye. (It is not clear, from the report, which group these three patients were in, but it is assumed that they were in the group of 24 patients recorded as having some useful vision.)

The visual acuity in the successfully irradiated eyes was as follows: 6/6, 10 patients; 6/9, 1 patient; 6/24, 2 patients; 6/36, 1 patient; 6/60, 2 patients; light perception, 1 patient. The remaining seven patients were still too young for any reasonable estimate of vision to be made.

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29. Stallard, H. B.: Comparative Value of Radium and Deep X-Rays in the Treatment of Retinoblastoma, Brit. J. Ophth. **36**:313, 1952; Irradiation of Retinoblastomas, Lancet **1**:1046, 1952; Treatment of Glioma Retinae (Retinoblastoma) by Radium, M. Press **114**:217, 1922.

Complications were as follows: cataract necessitating extraction, three patients; lens opacity, six patients; retinal exudates appearing from 7 months to 9 years after therapy, three patients; retinal hemorrhages, three patients, appearing 13 years after irradiation in one; diffuse choroidal and subretinal hemorrhage, one patient.

In the other series of patients reported in this article, the results were not so good. In Foster Moore's series, four of the five patients survived. In two of the patients radiation cataract and macular scarring developed but they had sufficient vision to enable them to earn a living. Two were blind.

Of the 21 cases collected from the literature, the data given in 4 were insufficient to allow a statistical study. Three of the patients had died, and seven were blind. Seven patients were considered to have a successful result.

Of the eight patients treated at Christie Hospital and the Holt Radium Institute, three had some "vision" and for five radiation failed. These patients were treated with 1.5- to 4.5 cm.-long radium needles inserted through the lids into the orbit. This technique gives extensive radiation to the globe.

Stallard describes in some detail the radium disks which he uses. These vary from 2 to 20 mm. in diameter, and their radium content ranges from 0.5 to 5 mg. He states that either radium salts or cobalt [30] may be used. A dose of approximately 2,500 to 3,500 rep to the apex of the neoplasm and a dose of from 6,000 to 8,000 rep at the base are generally required to destroy the retinoblastoma.

It is Stallard's opinion that the most efficient and least complicated method of treating a retinoblastoma which covers one-third of the globe or less is by the use of radium plaques designed to fit the curvature of the sclera and attached in the area of the retinoblastoma. If the tumor covers as much as one-half the globe, irradiation is of little value, for invariably the globe is destroyed during the process of destruction of the tumor.

The pathological changes which occur in retinoblastomas following treatment with radon seeds and radium disks are discussed by Stallard.[30] His observations are based on a study of serial sections of eight eyes containing irradiated retinoblastomas. The usual postirradiation changes of pyknosis, karyorrhexis, and atypical mitosis were found in the tumor cells. The blood vessels showed destruction of the endothelium and degenerative changes in the vessel walls. The adjacent normal retina showed degenerative signs in all layers, with swollen "ghost cells" in the nerve fiber layer and on the surface of the retina. In one eye there was a group of retinoblastoma cells with normal-staining nuclei which had apparently remained inactive for one year. The author states that a similar case, in which clumps of retinoblastoma cells remained viable for eight years without proliferation, has been reported.

Verhoeff [31] reports the case of a patient aged 36 who had a retinoblastoma in the lower outer quadrant treated with x-rays through a perforated lead plate that had been applied to the globe to protect the lens and anterior segment of the eye. Thirty-four years after the first x-ray treatment a scar at the site of the tumor could

30. Stallard, H. B.: Pathological Study of Retinoblastoma Treated with Radon Seeds and Radium Disks, Brit. J. Ophth. **36**:245, 1952.

31. Verhoeff, F. H.: Retinoblastoma Successfully Treated with X-Rays: Normal Vision Retained After 34 Years; Second Report on Case, A. M. A. Arch. Ophth. **48**:45, 1952.

still be seen, and the patient had a small posterior cortical cataract. His corrected visual acuity was 20/20. The author states that so long as the patient lives and maintains good vision he will continue to hold the record for duration of good vision after irradiation for retinoblastoma.

Sovik [32] presents the case histories of six children with retinoblastomas in a sibship of nine. This family is of particular interest, since 66% of its members are affected and the incidence of bilateral involvement is 100%. A detailed description of the pathological examination of 11 enucleated eyes is given, and the author presents evidence to support the theory that retinoblastomas originate in the outer nuclear layer.

An interesting case of bilateral retinoblastoma occurring in a premature infant who weighed 1,750 gm. at birth is reported by Hix and Danielson.[33] Examinations of this infant's fundi were made at weekly intervals from the 23d day after birth until the 3d month of life. On the 45th postpartum day, a diagnosis of retrolental fibroplasia was made and cortisone therapy was started. Fourteen days later, on Nov. 14, 1950, a slightly edematous, grayish appearance was noted in the macula of the left eye. On Nov. 29 a similar lesion was noted in the right eye. By Dec. 5 a probable diagnosis of bilateral retinoblastoma was made, but it was decided, because of the small size of the lesion, to postpone enucleation until a more characteristic appearance resulted. The child was discharged from the hospital on Dec. 14, but, in spite of precautions to assure adequate follow-up observation, was not seen again until Jan. 15, at which time the mass had increased markedly in both eyes. The right eye was removed, and the left eye was treated with x-rays. Histological examination revealed a retinoblastoma in the right eye. The authors state that, so far as they know, there is no other case in the literature in which a retinoblastoma has been followed since the time of its first clinical appearance.

In the fourth of a series of reports concerning the authors' experiences with tumors of the eye and adnexa, Swan and Hyman [34] discuss their experiences with tumors of the retina. Postinflammatory or post-traumatic proliferation, cystic conditions simulating retinal neoplasms, metastatic tumors of the retina, and phacomatoses with retinal involvement are comparatively rare.

The commonest primary neoplasm was retinoblastoma. Twenty-five patients with retinoblastoma have been observed during the past seven years. For 20 of these patients a complete history and examination were obtained. Twelve had bilateral retinoblastoma. Over half the eyes enucleated showed histological evidence of extraocular extension of the tumor. The total number of patients who were living after enucleation is not given, but it is stated that of 12 patients who had bilateral retinoblastomas, 5 either have shown evidence of extraorbital metastasis or have died of metastasis. A recurrence of the tumor has not been observed in any case in which the optic nerve was not involved. Six of the children with bilateral retinoblastoma have had one eye treated with x-rays. One patient is still in the process of receiving x-ray therapy. Of the other five, two have survived for more

32. Sovik, W. E.: Bilateral Retinoblastomas in 6 Siblings, Am. J. Ophth. **35**:1611, 1952.

33. Hix, I. E., Jr., and Danielson, R. W.: Bilateral Retinoblastoma in the Premature Infant, Am. J. Ophth. **35**:1647, 1952.

34. Swan, K. C., and Hyman, S.: Experiences with Tumors of the Retina, A. M. A. Arch. Ophth. **47**:416, 1952.

than five years, with retention of nearly normal visual acuity. Two patients have retained good visual acuity but have been observed for a shorter period. One patient had secondary glaucoma before irradiation was undertaken. Therapy was completed, but the eye was enucleated for relief of pain from the glaucomatous process. Histological study of the enucleated eye revealed that the tumor had been completely destroyed. The child has survived and is healthy, six years after enucleation.

Duc and Busti [35] describe three cases of retinal glioma and call attention to the frequent histological picture of polymorphism and the consequent difficulty in classifying a particular case under one type. The authors consider it desirable to follow enucleation with x-ray therapy to the orbit.

Angiomatosis Retinae.—Sœbø [36] describes a family five members of which had von Hippel-Lindau disease. An affected woman, married to an unaffected man, had six children, four of whom were males and two females. Of the children, three males and one female had von Hippel-Lindau disease. The disease in this family was inherited as a dominant characteristic, and therefore the affected members were told they should have no children.

The author stresses the difficulty in making the diagnosis of this disease in some instances and the poor prognosis for the patient. One patient had an apparently good effect from diathermy coagulation, but later the disease spread to other parts of the fundus and led to blindness. In a second patient, who was treated with diathermy, a retinal detachment developed immediately after the operative procedure.

The author states that reports in the literature seldom describe the disease as affecting both eyes but that in his series both eyes were affected in all patients.

A pedigree containing five verified cases and four doubtful cases of von Hippel-Lindau disease is presented by Møller.[37] He emphasizes the variable clinical picture of the disease and states that, for this reason, the hereditary factor is often overlooked. In the material examined in his study, inheritance was of an irregularly dominant type without sex linkage. Electrocoagulation of the angiomas appeared to yield the best results.

Guillaumat and Mercier [38] discuss the etiology, evolution, clinical picture, pathology, and treatment of angiomatosis retinae. They also report five new cases, in three of which treatment with diathermy coagulation was successful.

François and Coffyn [39] describe the case of a man aged 30 who was found to have a cerebellar angioma in 1944. At that time he had 4 D. of papilledema in each eye and visual acuity was reduced to 6/12. The hemangioma was extirpated. He recovered from the operation and was followed periodically. In 1948 the visual acuity in his right eye was reduced to 1/10. Examination of this eye revealed a peripheral angioma on the temporal side, with an extremely dilated vein and artery entering the lesion. The left eye was normal.

35. Duc, C., and Busti, A.: A Contribution to the Study of Retinal Tumors, Rass. ital. ottal. **21**:163, 1952.

36. Sœbø, J. A.: Von Hippel-Lindau's Disease, Acta ophth. **30**:129, 1952.

37. Møller, P. M.: Another Family with von Hippel-Lindau's Disease, Acta ophth. **30**:155, 1952.

38. Guillaumat, L., and Mercier, J.: Report on Five Cases of Angiomatosis Retinae and Therapeutic Considerations, Arch. opht. **12**:265, 1952.

39. François, J., and Coffyn, J.: Retinal Cerebellar Visceral Angiomatosis, or von-Hippel Lindau's Disease, Ann. ocul. **184**:206, 1951.

HYPERTENSION

The etiology of hypertensive cardiovascular disease remains one of the most perplexing problems in medicine. It is generally agreed that the cause of the disease can be determined in approximately 10% of persons with elevated diastolic blood pressure. Some causes are toxemia of pregnancy, disorders of the kidneys and adrenal glands, cerebral disturbances, and coarctation of the aorta. In the remaining 90% the cause of the elevated blood pressure is not known, and the condition is classified as essential hypertension.

In approximately 90% of patients with essential hypertension, the disease has a prolonged course, which is extremely variable but tends to progress toward failure of vascular adaptation and death from vascular disease. The patients are usually hyperreactors whose blood pressure varies to a striking degree. Under conditions of stress, their blood pressure is well above normal range, but under resting conditions it falls promptly to normal. Later, the pressure becomes elevated more frequently, almost constantly, and finally it no longer falls to normal during rest. Patients of this type are classified as having benign essential hypertension. In 5 to 10% of all patients with essential hypertension a rapidly deteriorating, necrotizing arteriolitis of the vascular system occurs. This condition is known as malignant hypertension.

It has generally been assumed that the initial defect of patients with essential hypertension is a constriction of the arterioles, which leads to an increase in the peripheral resistance to blood flow and an elevation of the systolic and diastolic pressures. These manifestations are followed by changes in the walls of the arterioles and a decrease in the diameter of their lumen.

Goldring,[40] in an interesting summary of the problem, points out that it is not even certain that an elevation of the blood pressure is the essential factor in this syndrome. He notes that the severity of the symptoms is not always proportional to the level of the blood pressure and that a reduction of the blood pressure by surgical or medical means does not always stop the advance of the vascular changes. He suggests that essential hypertension is caused by an unknown x-substance, which not only produces vasoconstriction and hypertension but also attacks the vessel walls. Thus, any means which is designed merely to lower the blood pressure, and does not eliminate or counteract the x-substance, will be ineffective in preventing the progress of the disease. He grants that this concept is controversial but states that a full acceptance of the thesis that an elevation of the blood pressure, regardless of the cause, produces arteriolar disease does not explain all the problems in essential hypertension.

Elderly persons with systolic atherosclerotic hypertension should be placed in a separate group. Their hypertension is not complicated by an increased peripheral resistance of the smaller arterioles and does not involve the diastolic pressure. In itself, the elevated systolic pressure is relatively harmless and requires no special treatment. It is true that the accompanying arteriosclerosis of the coronary, cerebral, or other peripheral vessels may be associated with atherosclerosis of the major vessels, but these complications can occur with normal or low systolic blood pressure.

40. Goldring, W.: Practitioner's Conference: Essential Hypertension, New York Med. (No. 11) **8**:16, 1952.

Elwyn,[41] in a discussion of hypertension, points out that the maintenance of normal blood pressure depends upon the resistance of the peripheral vessels as long as the cardiac output and blood volume remain normal. He thinks that the vessels in the splanchnic area are of primary importance in this system, for the smaller arteries and arterioles in organs such as the kidney, heart, and brain are not sufficient in number to influence appreciably the level of pressure. The vessels in the muscles of the limbs and trunk can also be ruled out, for they are normally constricted in the resting state but dilate six or eight times their normal size during muscular activity without appreciably altering the blood pressure. Therefore, it seems reasonable to assume that only the splanchnic circulation has a sufficient volume of small arteries and arterioles to maintain normal or elevated blood pressure effectively. It is his concept that essential hypertension is an inherited characteristic in which the spinal centers escape from the regulatory control of the hypothalamic centers. Thus, a state of greater irritability and vasospasm of the vessels in the splanchnic circulation is produced.

Wakerlin[42] states that in children of two hypertensive parents there is a 50% chance of essential hypertension developing in later life.

Elwyn[41] divides essential hypertension into three types: In the first, benign essential hypertension, the fundamental change is in the state of contraction of the small arteries of the splanchnic circulation. There is no abnormal constriction of the arteries of the kidney, brain, or retina. In the second, or intermediary, type, in addition to splanchnic contraction, there is cerebral and retinal vascular involvement. The third type is the malignant phase of essential hypertension, with malignant nephrosclerosis. In this type there is spastic contraction of the renal, cerebral, and retinal arteries, with production of cerebral symptoms, renal insufficiency, and arteriospastic retinopathy.

The changes in the fundus of the eye during the course of hypertension present two distinct pictures. The first, which is due to aging of the vessels, with associated arteriosclerosis and arteriolosclerosis, is the result of the excessive activity of the retinal vessels regulating the local blood flow against increased blood pressure. The second is arteriospastic retinopathy, which results from constriction of the retinal arteries.

Adler,[43] contrary to Elwyn's suggestions, thinks that essential hypertension is probably caused by a humoral agent which produces a vasoconstriction of all the peripheral vessels.

Schiff-Wertheimer[44] states that the factors which physiologically combine to produce stable blood pressure are (1) cardiac contraction, (2) total blood volume, (3) pulsatile contraction of the great vessels, and (4) peripheral resistance. The maintenance of equilibrium among these diverse factors is dependent upon a regulatory system, which includes reflex-initiating zones, nerve-regulating centers,

41. Elwyn, H.: Hypertension and Changes in the Fundus of the Eye, Bull. New York Acad. Med. **28**:145, 1952.

42. Wakerlin, G. E.: Pathogenesis and Treatment of Essential Hypertension, M. Clin. North America, January, 1952, p. 129.

43. Adler, F. H.: Rôle of the Sympathetic Nervous System in the Genesis of Vascular Hypertension and Its Effect upon the Eye, Acta XVI Cong. Ophth., London **1**:1, 1950.

44. Schiff-Wertheimer, S.: Rôle of the Sympathetic in Arterial Hypertension and Its Effect on the Retinal Vessels, Acta XVI Cong. Ophth., London **1**:22, 1950.

and the ill-understood action of certain endocrine glands. He states that it is impossible to specify exactly what role is played by the sympathetic system in the maintenance or aggravation of arterial hypertension.

The occurrence of unexplained, or essential, hypertension in children is extremely rare.[45] In the majority of children hypertension is associated with renal disease, most frequently in the form of acute or chronic glomerulonephritis. Occasionally, hypertension is encountered with diseases of the endocrine system, particularly pheochromocytomas and disorders of the adrenal cortex. It can result, also, from infection or damage to the central nervous system, as well as from increased intracranial pressure due to any cause. Occasionally children with diseases of the heart or greater vessels will also have hypertension.

Attempts have again been made this year to classify and correlate the retinal changes with vascular changes elsewhere in the body in patients with hypertension.[46] It is generally agreed that there is a statistical correlation between the retinal and the systemic vascular changes, but it is frequently pointed out that in a given case the retinal changes do not always reflect a true picture of the systemic vascular lesions.

Wendland [47] studied 80 patients who had undergone sympathectomy for essential hypertension. The severity of retinal arteriolosclerosis, as seen with the ophthalmoscope, was compared with the degree of renal arteriolosclerosis, as determined by histological examination of biopsy specimens of the kidney. The degree of change in both the retina and the kidney was graded on the basis of 1 to 4. In 86% of the patients the sclerosis in the eyes and that in the kidneys were of equal degree or differed by not more than one grade. The changes in the retinal vessels, on the whole, were somewhat greater than those in the kidney.

The author states that the results of his investigation are in accord with the view that renal arteriolosclerosis is either the direct result of hypertension or an independent process enhanced by hypertension. The theory that renal arteriolosclerosis frequently plays a role in the etiology of hypertension through the alteration of renal hemodynamics and liberation of a pressor substance is not substantiated by the findings in this study.

The study of retinal vessels by means of ophthalmodynamometry continues to be of considerable interest in Europe but, as yet, has been reported only rarely in the United States. Weigelin and Althause [48] compared the changes in the brachial blood pressure with the changes in the central retinal artery in 60 healthy persons

45. McCrory, W. W., and Nash, F. W.: Hypertension in Children: A Review, Am. J. M. Sc. **223**:671, 1952.

46. Lijó Pavía, J.: A Simple Classification of Retinal Angiopathy in General Arterial Hypertension, Am. J. Ophth. **35**:404, 1952. Fischer, F.: Effect of Acute and Chronic Diffuse Glomerulonephritis on the Eye, Med. Monatsschr. **5**:755, 1951; Classification of Ocular Findings in Malignant Hypertension and Malignant Nephrosclerosis (Volhard), München med. Wchnschr. **94**:789, 1952. Tilling, W.: Follow-up Studies in Angiospastic Retinitis with Renal Insufficiency, ibid. **94**:793, 1952. Macaskil, J.: Retinal Changes in Hypertension, Edinburgh M. J. **59**:334, 1952. Leishman, R.: Retinal Vessels in Hypertensive Disease, Proc. Roy. Soc. Med. **45**:419, 1952.

47. Wendland, J. P.: Relationship of Retinal and Renal Arteriolosclerosis in Living Patients with Essential Hypertension, Am. J. Ophth. **35**:1748, 1952.

48. Weigelin, E., and Althause, H.: Investigation of the Central Retinal Artery Pressure in Normal Subjects by Cold Pressor Tests (After Hines and Brown), Ophthalmologica **124**:1, 1952.

after the cold pressor test. They found that there was an average increase in the brachial blood pressure of 7±7.2 mm. Hg diastolic and 5.8±4.8 mm. Hg systolic. In the central retinal arteries the blood pressure increased an average of 4.5±2.7 mm. Hg diastolic and 5.5±4.3 mm. Hg systolic. Initial values were regained one to two minutes after the end of stimulation. The authors think that the cause of increase in blood pressure in the central retinal artery is, in most cases, an active contraction of the intracranial vessels, rather than an increase in forcing power.

Lijó Pavía,[49] in an interesting study, reports the results of cinematographic records of arterial pulsation in various conditions. He found that with arterial pulsation induced by pressure on the globe, the central retinal artery underwent active contraction during cardiac diastole and dilatation during systole. If 10 is taken as a unit of time for the duration of these two phases, it was found that in patients with normal blood pressure the contraction lasted 2.5 and the dilatation about 7.5. Thus, the proportion was about 1 : 3. In patients with hypertension the phases of contraction and dilatation ranged from 4 to 3.33 and 6 to 6.66 respectively. The proportions were thus 1 : 1.5 and 1 : 2.

The value of Bailliart's retinohumoral ratio as a diagnostic and prognostic sign in vascular hypertension was studied by DuBois-Poulsen and Miller.[50] This ratio is the proportion between the diastolic retinal pressure and the diastolic systemic pressure and is normally 0.5. In 154 patients with malignant hypertension, 86% showed a ratio of over 0.50. Of 102 patients with benign hypertension, 72% showed a ratio of 0.50 or under. Of 40 patients with benign hypertension which was becoming malignant, 70% showed a ratio over 0.50. A comparison of the ophthalmoscopic changes as classified by Wagner with the retinal-humoral ratio showed that the latter gave an earlier indication of severe vascular change.

Miller and his co-workers[51] studied the effects of subdiaphragmatic sympathectomy and decapsulation of the kidneys in 82 patients with arterial hypertension. The retinal pressure and ophthalmoscopic findings were recorded in all cases. A rise in the retinal arterial pressure, especially if it occurred without a corresponding change in the general arterial pressure, constituted an unfavorable prognostic sign, even when the ophthalmoscopic changes were negligible.

Weigelin and Müller[52] studied changes in the retinal and cerebral vascular circulation by determining the retinal vascular pressure and the systemic (brachial) blood pressure. These determinations have enabled them to discriminate between spastic and organic processes in the vessels. They have also assembled data which aid in the localizing of intracranial lesions.

Treatment.—In any discussion of the treatment of high blood pressure, one should differentiate hypertension caused by kidney or adrenal disease, coarctation of the aorta, toxemia of pregnancy, and systolic hypertension of the arteriosclerotic

49. Lijó Pavía, J.: Pulsations Provoked in the Central Retinal Artery Documented by Cinematography, Acta XVI Cong. Ophth., London **1**:422, 1950; Induced Pulsations in the Central Retinal Artery of Cardiac Patients, Am. J. Ophth. **35**:585, 1952.

50. DuBois-Poulsen, A., and Miller, H. A.: Comparative Study of Anatomical and Sphygmoscopic Retinal Changes in Arterial Hypertension, Acta XVI Cong. Ophth., London **1**:381. 1950.

51. Miller, H. A.; Lévy, M., and Sapir, M.: Diastolic Tension in Retinal Arteries and Sympathectomy in Arterial Hypertension, Bull. Soc. opht. France **64**:412, 1951.

52. Weigelin, E., and Müller, H. K.: Practical Significance of Blood Pressure Measurements of the Central Retinal Artery, Docum. ophth. **5-6**:357, 1951.

type from essential hypertension. The treatment of elevated blood pressure in the first conditions is frequently very satisfactory, for in many instances the removal of the offending agent may produce a permanent lowering of blood pressure. The situation in essential hypertension is not nearly as encouraging.

Corr,[53] in a discussion of this problem, states:

> The treatment of essential hypertension requires individualization by the physician who usually assumes the role of a wise counselor but who, in the face of serious complication, such as malignant hypertension, may be obliged to resort to rather desperate therapeutic measures, including rigid diets, prolonged pyrogen or other presumably specific therapy, or sympathectomy. There is no really satisfactory treatment for high blood pressure.

Reports [54] during the past year have indicated that such diverse treatments as diet, sympathectomy, drugs which block the sympathetic nervous system, subtotal adrenalectomy, and pyschotherapy may relieve subjective symptoms, and in some instances may even produce a remission of retinal hemorrhages and papilledema. They may also temporarily reduce the level of blood pressure and prolong life for a few years. However, none of these treatments either permanently reduces blood pressure or stops the progress of the disease in most instances.

ATHEROSCLEROSIS

A major trend in medicine at present is a change in attitude toward the problems of the aged. Prior to the advent of antibiotics, the study and treatment of infectious diseases consumed a major portion of the time and energy of physicians. Now that mortality from many of these diseases has been appreciably reduced, the average expectation of the duration of human life has been increased. Thus, the problems of the aged assume proportionately greater importance.

Medalia and White [55] reviewed the autopsy protocols of 1,251 patients who died between the ages of 50 and 90 years. Cardiovascular-renal lesions, particularly coronary sclerosis, aortic atherosclerosis, and vascular nephritis, were the diseases most frequently found in the advanced age group.

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53. Corr, W. P.: Management of High Blood Pressure, M. Clin. North America, July, 1952, p. 1013.

54. Rosenheim, L. M.: Discussion of the Medical Treatment of Hypertension, Proc. Royal Soc. Med. **45**:269, 1952. Kauntze, R.: Discussion of the Medical Treatment of Hypertension, ibid. **45**:271, 1952. Kempner, W.: Treatment of Retinopathy in Kidney Disease and Hypertension and Arteriosclerotic Vascular Disease with the Rice Diet, Ophth. ibero-am. **13**:1, 1951. Davis, L.: Physiological Principles Underlying the Treatment of High Diastolic Essential Hypertension by Thiocyanates and Sympathectomy, Lancet **1**:1171, 1952. Dawson, A. M.: Dietary Treatment of Hypertension, M. Press **114**:509, 1952. Reversibility of Hypertension, Lancet **2**:969, 1952. Locket, S.; Swann, P. G.; Grieve, W. S. M., and Player, H. P.: M. & B. 1863, A Homologue of Hexamethonium in the Treatment of Hypertension, Brit. M. J. **1**:254, 1952. Wakerlin.[42] Rosner, S.: Bilateral Cervical Sympathectomy with Stellate Ganglionectomy in Essential Hypertension, J. Nerv. & Ment. Dis. **115**:526, 1952. Atkins, H. J. B.: Rôle of the Sympathetic System in the Genesis of Vascular Hypertension and Its Effects upon the Eye, Acta XVI Cong. Ophth., London **1**:103, 1950. Thorn, G. W.; Harrison, J. H.; Merrill, J. P.; Criscitiello, M. G.; Frawley, T. F., and Finkenstaedt, J. T.: Clinical Studies on Bilateral Complete Adrenalectomy in Patients with Severe Hypertensive Vascular Disease, Ann. Int. Med. **37**:972, 1952. Wilkins, R. W.: New Drug Therapies in Arterial Hypertension, ibid. **37**:1144, 1952.

55. Medalia, L. S., and White, P. D.: Diseases of the Aged, J. A. M. A. **149**:1433, 1952.

In the past it has been assumed that atherosclerosis was an inevitable consequence of aging. Several authors[56] point out that atherosclerosis is a disease process most probably related to an alteration of cholesterol metabolism, and that it may occur in young, as well as in elderly persons. They also state that these vascular lesions are reversible, not only the juvenile fatty streaks, but also the more fully developed atherosclerotic lesions seen in older patients.

Since the retinal and choroidal changes produced by arteriosclerosis are responsible for a high percentage of visual impairment in elderly persons, it might be of value to review briefly some of the present concepts of the pathogenesis of atherosclerosis.

Blumgart[57] points out that many of the results of investigations on atherosclerosis have been difficult to interpret and that they frequently contradict one another. However, from researches involving different techniques in different experimental subjects, a dim outline of the nature of the disorder is beginning to appear.

The constant histological finding of lipids in atheromatous lesions suggests that these changes are related to a defect in the cholesterol metabolism. In support of this theory, many investigators have produced atherosclerosis in rabbits by feeding them large amounts of cholesterol. Similar lesions have been produced in chickens by diets containing more moderate amounts of cholesterol. Further evidence to support this theory has been the finding that serum cholesterol levels in patients with atherosclerotic coronary disease are, in general, somewhat higher and tend to fluctuate more widely than in others not so afflicted. Because of these observations attempts have been made to lower the serum cholesterol levels by dietary and other means.

The significance of these findings is not entirely clear, however, in the light of other data. Some workers found that arteriosclerosis did not always occur in rabbits even when they were fed very large amounts of cholesterol. Moreover, cholesterol feedings in animals other than the rabbit did not always result in the characteristic lesions, and spontaneous arteriosclerosis does occur in chickens despite cholesterol-free, fat-poor diets. In addition, many persons with widespread involvement of the coronary and other arteries have normal cholesterol and phospholipid values; conversely, elevated values may be found in those not so affected.

In regard to the dietary management of the disease, it has been pointed out that persons who consume as little as 200 mg. of cholesterol a day do not always show a reduction in this substance in their serum. This is not altogether surprising, since cholesterol can be synthetized in the body from acetate, which is available as a result of the metabolism of fats, glucose, and protein.

A new approach to the study of the problem has been introduced by Gofman, Jones, and their associates,[58] who point out that the major lipids in the blood are

56. Stamler, J.: Pathogenesis and Therapy of Atherosclerosis, M. Clin. North America, January, 1952, p. 177. Page, I. H.: Low Cholesterol—Low Fat Diets in Prevention and Treatment of Atherosclerosis, ibid., January 1952, p. 195. Zinn, W. J., and Griffith, G. C.: Atherosclerosis: A Preventible Disease, ibid., July 1952, p. 1001. Wakerlin, G. E.: Recent Advances in the Pathogenesis and Treatment of Atherosclerosis, Ann. Int. Med. **37**:313, 1952.

57. Blumgart, H. L.: Blood Lipids and Atherosclerosis, Editorial, Am. J. Med. **11**:271, 1951.

58. Jones, H. B.; Gofman, J. W.; Lindgren, F. T.; Lyon, T. P.; Graham, D. M.; Strisower, B., and Nichols, A. V.: Lipoproteins in Atherosclerosis, Am. J. Med. **11**:358, 1951.

transported in the form of giant, lipoprotein molecules of several types, which contain glyceryl esters, cholesterol, cholesterol esters, phospholipids, and fatty acids. By the use of the analytical ultracentrifuge, they segregated these molecules into various groups according to their densities. For convenience and identification, the densities of the molecules were tabulated according to S_f units (Svedberg's flotation units). The major neutral fat (glyceryl ester)-bearing molecules are those of S_f 17 and higher, and in general, the major cholesterol-bearing molecules are those of S_f 17 and lower.

They have shown that in rabbits minimal or no atherosclerosis develops with blood cholesterol levels as high as 5,000 to 10,000 mg. per 100 cc. when cholesterol is transported in the form of molecules primarily of the S_f 40 to S_f 100 and higher classes. However, atherosclerosis regularly develops in animals with much lower blood cholesterol levels when transportation occurs in molecules of the S_f 10 to the S_f 30 class.

Likewise, the serum samples of normal patients were compared with those of patients who had myocardial infarcts of arteriolar-sclerotic origin. In the atherosclerotic patients this revealed a correlation two to four times as great with the S_f 12 to S_f 20 lipoprotein levels as with the total serum cholesterol levels.

The influence of dietary restriction of fats and cholesterol was studied in a group of 56 patients with myocardial infarctions whose initial S_f 12 to S_f 20 lipoprotein levels were above 80 mg. per 100 cc. The level in 42 of these patients remained above 80 mg. per 100 cc., and of this group 16 had recurrences of their myocardial lesions. Fourteen patients whose levels fell below 70 mg. per 100 cc. had no recurrence of their myocardial infarction.

Changes in the blood lipids and lipoproteins at various ages were also studied. One hundred forty normal boys and girls, ranging in age from birth to 15 years, were studied. There was no correlation between the different levels and sex or age in this group. Concentrations lower than 30 mg. per 100 cc. S_f 12 to S_f 20 lipoproteins was observed in 90% of the children, and 75% of the group had levels below 20 mg. per 100 cc. Men and women both showed similar low levels of S_f 12 to S_f 20 lipoproteins up to the age of 25. The male population underwent a striking transformation between the age of 25 and 30, when S_f 12 to S_f 20 levels became elevated from a median concentration of 28 mg. to 39 mg. per 100 cc. Beyond the age of 30 the clinically normal male population showed no further significant change through the 60th year. The normal female did not undergo the striking change between the ages of 25 and 30 that was seen in the male. The S_f 12 to S_f 20 level in the female population increased slowly and steadily over the entire 25- to 60-year span. A level essentially identical with that attained by the male population at 30 years of age was reached by the female during the 50- to 60-year period. These findings are closely correlated with the well-known sex difference in clinical sequelae of atherosclerosis as it affects persons below the age of 50.

One encouraging lead has emerged from the pharmacological treatment of arteriosclerosis. Seventy-five patients were treated with parenteral injections of 25 to 100 mg. of heparin once or twice a week. There was great individual variation in the lipoprotein response to treatment, but in all cases there was an alteration in the serum in the direction of normality. The latter clue should be of particular significance for ophthalmologists who are interested in the treatment of senile macular degeneration.

RETINAL VASCULAR TONE

It is generally accepted that the cerebral and retinal blood vessels do not always parallel the degree of constriction or dilatation of the vessels elsewhere in the body. It is also known that the cerebral and retinal vessels do not respond to vasodilator and vasoconstrictor drugs in the same manner as do vessels of the skin or the visceral vascular beds.[59] For this reason, Scheinberg and Jayne [60] reviewed the factors influencing cerebral blood flow and metabolism. This report should be of particular interest to ophthalmologists. The authors used the Kety and Schmidt nitrous-oxide technique to determine cerebral blood flow, and the differences in the oxygen content of the arterial and the venous cerebral blood to estimate the cerebral oxygen consumption.

The various factors which influence the cerebral blood flow are listed in Table 4.

Krasno and Ivy [61] claim that the change after sublingual administration of glyceryl trinitrate in the frequency in which flickering light appears to fuse (flicker fusion frequency) sharply differentiates persons with normal cardiovascular systems from patients with coronary and/or hypertensive disease, and that this test may be useful in detecting and evaluating such diseases. Keys and Simonson [62] have denied these claims on the basis of a detailed analysis of the original publication of Krasno and Ivy and a study of 145 clinically healthy "normal" men and 110 men with cardiovascular disease. They state that all categories of men showed higher fusion flicker frequency values when they were tested in the supine position than in an upright position, but the response to glyceryl trinitrate was substantially the same in the two groups. They conclude that the glyceryl trinitrate flicker fusion test cannot be recommended for the screening or detecting of persons with cardiovascular disease.

The response of the retinal vessels to benzazoline (Priscoline) in various vascular conditions has been determined by angioscotometry by Cholst and his co-workers.[63] Benzazoline is a benzyl-imidazoline drug that has two actions on the peripheral vascular system: In small doses it exerts a histamine-like action locally on the blood vessels, and in larger doses it produces an adrenergic block. The normal angioscotoma was platted for each subject, and then an intravenous injection of 50 mg. of benzazoline was given over a one-minute interval. The angioscotoma was then remapped every five minutes. The maximum effect of the drug was found to occur 10 to 15 minutes after injection, and the maximal dilatation lasted from 10 to 30 minutes. Tests were made on 12 normal persons, as controls, and on 20

59. Bailliart, P.; Jordan, F., and Heyrauch, J.: Cerebellar and Retinal Circulation, Presse méd. **60**:805, 1952.

60. Scheinberg, P., and Jayne, H. W.: Factors Influencing Cerebral Blood Flow and Metabolism: A Review, Circulation **5**:225, 1952.

61. Krasno, L. R., and Ivy, A. C.: Response of the Flicker Fusion Threshold to Nitroglycerine and Its Potential Value in Diagnosis, Prognosis, and Therapy of Subclinical and Clinical Cardiovascular Disease, Circulation **1**:1267, 1950.

62. Keys, A., and Simonson, E.: Flicker Fusion Frequency and Its Response to Nitroglycerine in Normal Subjects and in Patients with Cardiovascular Disease, Circulation **5**:215, 1952.

63. Cholst, M. R.; Schilback, H. F.; Handelsman, M. B., and Levitt, L. M.: Response of the Retinal Vessels to Priscoline in Various Vascular Conditions: Study I, Am. J. Ophth. **35**:191, 1952.

persons with various vascular lesions (2 with hypertensive cardiovascular disease, 2 with essential hypertension, 3 with chronic glomerulonephritis, 3 with advanced arteriosclerosis, and 4 with diabetes without retinopathy). The results were as follows: Normal persons, as well as patients with mild arteriosclerosis, revealed a good response to benzazoline. Those with advanced retinal arteriosclerosis showed a poor response.

TABLE 4.—*Factors Which Influence the Cerebral Blood Flow*

	$CMRO_2$ *	CVR †
Group 1		
Apprehension	Normal	Slightly increased
Induced fever	Normal	Slightly increased
Hyperthyroidism	Normal	Normal
Essential hypertension	Normal	Increased
Stellate block	Normal	Normal
Nicotinic acid	Normal	Normal
Intravenous use of procaine	Normal	Slightly increased
Histamine	Normal	Decreased
Schizophrenia	Normal	Normal
Insulin hypoglycemia	Decreased	Decreased
Uremia	Decreased	Normal
Desoxycorticosterone glucoside	Normal	Normal
Toxemia of pregnancy	Normal or decreased	Increased
20° head-up tilt	Normal	Decreased
Group 2		
CO_2 (5-7%)	Normal	Decreased
Diabetic coma	Decreased	Decreased
Anoxia (10% O_2)	Normal	Decreased
Anemia of acute blood loss	Normal	Decreased
Cerebral hemangioma	Normal	Decreased
Papaverine	Normal	Decreased
Thiopental anesthesia	Decreased	Decreased
Sleep	Normal	Decreased
Group 3		
Hyperventilation, O_2 (85-100%)	Increased Normal	Increased Increased
Polycythemia	Normal	Increased
Motionless standing	Normal	Decreased
Increased intracranial pressure	Decreased	Increased
Cerebral vascular disease	Normal or decreased	Increased
Heart failure	Decreased	Increased
Aminophylline	Normal	Increased
Caffeine	Normal	Increased
Myxedema	Decreased	Increased
Pernicious anemia	Decreased	Increased
Diabetic acidosis	Decreased	Increased
Thiopental narcosis	Decreased	Increased
Neurosyphilis	Decreased	Increased
Corticotropin or cortisone	Decreased	Increased

* $CMRO_2$ represents cerebral oxygen consumption.
† CVR represents cerebral vascular resistance.

In a second study, the authors [64] determined the response of the retinal vessels to benzazoline in patients with diabetes mellitus. They found a good response in

64. Cholst, M. R.; Schilback, H. F.; Handelsman, M. B.,. and Levitt, L. M.: Response of the Retinal Vessels to Priscoline in Diabetes Mellitus: Study II, Am. J. Ophth. **35**:375, 1952.

10 patients who had no retinal exudates and only a fair response in 5 other patients without exudates. Twelve patients who had retinal exudates showed a poor response.

Stern [65] was also impressed with the value of this drug in three patients with retinal angiospasm but found it ineffective in two patients with occlusion of the central retinal artery.

De Gaspare [66] examined the behavior of Goldman's artificial scotoma and angioscotoma under the following conditions: after inspiration of (1) pure oxygen at atmospheric pressure, (2) oxygen-poor mixtures, (3) a mixture of air and CO_2; after amyl nitrite; after injection of a mixture of nicotinic acid and after an injection of epinephrine. The results show that there is no exact parallel between the changes in amplitude of the angioscotoma and those of the artificial scotoma. The angioscotoma is dependent not only on the state of functional activity of the visual neurons but also on the caliber of the retinal vessels, whereas the artificial scotoma depends exclusively on the former. It was therefore concluded that the use of the artificial scotoma is more adequate for the study of the functional activity of the visual neurons.

The effect of Hydergine (a combination of three substances from the ergotoxine group) on blood pressure, pulse rate, intraocular pressure, and angioscotoma was observed by Šimková and Zahn [67] in 10 normal controls and in 10 persons with arteriosclerosis or hypertension of mild degree without retinopathy, and in 10 patients suffering from hypertension due to various causes or arteriosclerosis with retinopathy. The angioscotoma was markedly reduced (56 to 80%) in 40 to 45 minutes after the administration of 0.3 mg. of Hydergine subcutaneously, particularly in patients with initial values that were pathological. No significant change in the caliber of the blood vessels was noted with the ophthalmoscope. It is suggested that a decrease of congestion in the perivascular areas of the retina is brought about by this drug and that this improvement in retinal blood supply reduces the angioscotoma.

Drew and Petrohelos [68] measured the retinal arterial pressure in two cases of thrombosis of the internal carotid artery before and after stellate ganglion block and found that the pressure rose from 10/75 to 62/131 after block in one case and from 5/40 to 32/68 in the second case.

The influence of drugs of the nitrite group—benzazoline (Priscoline) and nicotinic acid given systemically or by retrobulbar injection—and the cold pressor test of Hines and Brown on the degree of retinal vascular dilatation has been studied.[69]

65. Stern, J. J.: A New Vasodilator in Ophthalmology, Am. J. Ophth. **35**:187, 1952.

66. de Gaspare, P. F. F.: Behavior of Goldman's Artificial Scotomata and of Angioscotomata in Various Experimental Conditions, Boll. ocul. **31**:157, 1952.

67. Šimková, M., and Zahn, K.: Effect of Hydergine on Retinal Circulation, Ophthalmologica **124**:39, 1952.

68. Drew, A. Z., and Petrohelos, M. A.: A New Technique for Evaluating Stellate Ganglion Block: A Preliminary Report, Univ. Michigan M. Bull. **17**:282, 1951.

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The influence of infrared irradiation, microdiathermy and hot compresses on the retinal vessels also has been determined.[70]

Huerkamp[71] describes a simple, rapid procedure for measuring the width of the retinal vessels. He uses indirect ophthalmoscopy. A set of thin wires with dulled surfaces, 0.05 to 0.5 mm. thick, are placed in a tube in the focal plane of a +13.00 D. lens (approximately 7.7 cm. from the lens). The size of the retinal vessels can be easily compared with the sets of wires.

Using this technique, the author[72] observed constriction of the retinal vessels in man and animals who were exposed to hyperventilation or stimulation of the sympathetic nerves. Lack of oxygen over long periods, as in exposure to high altitudes, caused an increase in number and length of retinal blood vessels in rabbits. Experimental anemia temporarily decreased the length and number of the vessels.

Sautter[73] states that peristasis means widening of the afferent part of the vascular system behind a spastic arterial constriction. It is preceded by narrowing of the arterial system. When the spasm ceases, relaxation follows, and small hemorrhages and exudates occur, indicating damage to the vascular epithelium by the preceding anoxia. Vascular dilatation without preceding spasm will never be followed by hemorrhage, although there may be exudates due to osmotic changes in the tissue. In complete occlusion of the central retinal artery there is retinal edema and no hemorrhage. The author demonstrates these changes in the retinal vessels of rabbits by injecting epinephrine into the vitreous and at the same time injecting trypan blue intravenously.

The survival time of retinal cells when deprived of their blood supply is discussed by Smith and Baird.[74] Two techniques were used to produce retinal ischemia. In the first, the central retinal artery and the long and short posterior ciliary vessels were cut. In the second, the intraocular pressure was increased by introducing sterile fluid into the eye under sufficient pressure to express all blood from the vessels. The pressure was controlled and maintained at a constant level of 100 mm. Hg by using a pressure bottle connected to a mercury manometer.

When the vessels to the retina were cut, degenerative changes were first noted in the bipolar cells after 15 to 20 minutes, in the ganglion cells after 20 to 30 minutes, and in the rods and cones after 20 to 30 minutes.

In the second group, in which retinal ischemia was produced by increased intraocular pressure, the results closely paralleled those of the first group, as to both rate and type of degeneration. If the ischemia lasted for 10 minutes or less, the retina was normal even after 21 days. Most of the ganglion and bipolar cells degenerated and were absorbed in 21 days, when the retinal blood supply was

70. Yamagish, H.: Effect of Physical Influences on Retinal Arterial Pressure, Acta Soc. ophth. jap. **55**:187, 1951.

71. Huerkamp, B.: Measurement of Rapid Changes in Diameter of Retinal Blood Vessels, von Graefes Arch. Ophth. **152**:485, 1952.

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74. Smith, G. G., and Baird, C. D.: Survival Time of Retinal Cells When Deprived of Their Blood Supply by Increased Intraocular Pressure, Am. J. Ophth. **35**:(no. 5, Pt. 2) 133, 1952.

obliterated for 20 minutes. If anemia lasted for more than 30 minutes, the retina degenerated completely and was reduced to a thin layer of irregularly arranged cells in 21 days.

Sautter and Seitz [75] studied the blood supply of the lamina cribrosa in the rabbit by injecting trypan blue in the circulation. The optic nerve was ligated on one side, and all vessels entering the globe posteriorly except the central retinal artery were cut on the other. On histological examination they found that the lamina cribrosa is vascularized by branches from the central retinal artery. The scleral arterial circle of Zinn gets its blood supply from anastomosis of vessels from the central retinal artery and the posterior short ciliary arteries. Glomus cells were found where vessels from both the short posterior ciliary arteries and the central artery gave off branches to enter the arterial circle of the sclera.

RETINAL VEIN OCCLUSIONS

Wright [76] discusses in some detail modern concepts of the pathogenesis of thrombosis. He also evaluates some of the newer anticoagulants, such as ethyl biscoumacetate (Tromexan; 3,3'-carboxymethylene bis-[4-hydroxycoumarin] ethyl ester), phenylindanedione (Danilone), 4-hydroxycoumarin anticoagulant No. 63-B, and Parotil, a synthetic polysulfuric ester of polyanhydromannuronic acid.

Hope-Robertson [77] reports two patients with thrombosis of the central retinal veins. One of these sustained a relatively minor injury seven days before the onset of blurred vision. The second patient was in an automobile accident and received no severe injury. Four days later he noted blurring of vision. The author thinks that the typical venous occlusion was related in some way to the accident.

Cascio [78] investigated the prothrombin time, erythrocyte sedimentation rate, blood heparin, plasma protein, and cholesterol in 13 cases of thrombosis of the central retinal vein. The prothrombin time was higher than normal in 5, and the heparin content of the blood was subnormal in 4; the cholesterol content was elevated in 4, and the plasma protein was elevated in 1. The author concludes that this condition is due to a thrombotic diathesis.

Gasparri [79] reports the results of ethyl biscoumacetate therapy in 25 cases of retinal venous thrombosis. In 64% of these cases a good result was obtained. It was noted that while it is necessary to control the prothrombin time during administration of the drug, the secondary effects, such as hematuria and hemorrhagia, are relatively mild compared with those of bishydroxycoumarin.

75. Sautter, H., and Seitz, R.: A Study of the Relationship Between the Central and Ciliary Vascular Systems in the Region of the Lamina Cribrosa, von Graefes Arch. Ophth. **152**:413, 1952.

76. Wright, I. S.: The George E. Brown Memorial Lecture: The Pathogenesis and Treatment of Thrombosis, Circulation **5**:161, 1952.

77. Hope-Robertson, W. J.: Thrombosis of the Central Retinal Vein Following Injury: Report of 2 Cases, New Zealand M. J. (Supp.) 1952, p. 22.

78. Cascio, G.: Some Aspects of the Blood and Metabolism of Subjects with Thrombosis of the Central Retinal Vein: Prothrombin Time, Ann. ocul. **185**:640, 1952.

79. Gasparri, F.: Treatment of Venous Thrombosis of the Retina with Tromexan, Gior. ital. oftal. **5**:395, 1952.

(To Be Concluded)

Correspondence

MYCOTIC INFECTION

To the Editor:—In the paper by Harry L. Birge, entitled Ocular Aspects of Mycotic Infection, published in the March 1952 issue of the ARCHIVES, pages 354 to 382, a few errors appeared. Their correction should increase the value of this comprehensive review.

Page 358: In the classification of Thallophyta, under E, the synonym for Blastomyces brasiliensis is B. paracoccidioides (not pseudococcidioides). The lesion has been confused in South America with coccidioidomycosis but has been definitely established as a separate disease.

Under I, the term should be "Madura foot." The fungus most frequently found as the cause of this disorder in the United States is Monosporium apiospermum. In other parts of the world aerobic Actinomycetaceae (Nocardias) produce Madura foot (synonym mycetoma pedis).

Page 359: Contrary to the author's statement, most pathogenic fungi do not produce filaments in tissue but produce yeast-like cells (Histoplasma capsulatum, Blastomyces dermatitidis, and B. brasiliensis) or spherules (Coccidioides immitis). Only in Candida are pseudomycelia formed, and hyphae are seen in such rare invaders as Aspergillus.

Page 360: The use and value of the trichophytin tests are restricted.

Page 361: Concerning the agglutination test, extensive work has been published on complement fixation and precipitin reactions in histoplasmosis and coccidioidomycosis, but no reliable agglutination test is used for the diagnosis of moniliasis, blastomycosis, and coccidioidomycosis.

Page 362: The various names, such as Tinea pedis and Tinea manuum, refer to the localization of the disease, but not to the invading organisms, which may be one of the three groups of dermatophytes (Microsporum, Trichophyton, and Epidermophyton). Dermatologists very definitely believe that tineas are produced by fungi, but sensitization to fungus may later produce allergic reactions (trichophytid, etc.).

Page 363: Trichomycosis axillaris, or lepothrix, is a harmless disease of axillary hair caused by Nocardia tenuis and has nothing in common with infections with Leptothrix, which are iron bacteria.

Page 368: The term Blastomyces dermatitidis is indeed a misnomer but one in general use. It then becomes hazardous to speak of Blastomyces as baker's yeast. The author probably has in mind yeasts of the genus Saccharomyces.

Page 370: "Granuloma paracoccidioides": Coccidioidosis is a disease caused by a protozoan parasite, but the fungus disease which is compared with granuloma paracoccidioides is coccidioidomycosis.

Page 372: Histoplasmosis is not rare and usually not fatal. Probably 20,000,000 people in the United States have had the disease, but very few have died. In fact, it is one of the most benign infectious diseases in man, and only in the exceptional case is it fatal.

Contrary to the author's statement, Histoplasma has been cultured repeatedly from soil.

Dr. Birge certainly must realize that he could detect more mistakes if I should write on eye diseases than I have had to point out in his excursion into mycology.

JAN SCHWARZ, M.D.
Cincinnati General Hospital
Cincinnati 29.

Obituaries

SYLVESTER JUDD BEACH, M.D.
1879-1953

On Feb. 10, 1953, there passed from our midst one of America's best-known and admired ophthalmologists, Dr. Sylvester Judd Beach. Though stricken with a cerebral hemorrhage in 1948 which left him partly aphasic, he met his illness with great fortitude, and never gave up in the battle to regain his health.

Sylvester Judd Beach, son of Seth Curtis Beach and Frances Hall Beach, was born in Dedham, Mass., on April 7, 1879. He was graduated from Exeter Academy in 1897, from Harvard College in 1901, and from the Harvard Medical School in 1905. He began the practice of ophthalmology in Augusta, Maine, in 1909 and removed to Portland, Maine, in 1920, where he continued in active practice until his last illness.

Dr. Beach early in his career began to take an interest in and devote much time to the affairs of ophthalmology as a whole. Few ophthalmologists have held as many important offices in American ophthalmology. He was a member of the American Board of Ophthalmology from 1930 to 1948, serving as secretary from 1944 to 1948.

He was a member of the council of the American Ophthalmological Society from 1936 to 1940 and was elected vice-president in 1943 and president in 1944. He was Chairman of the Section of Ophthalmology of the American Medical Association in 1939. He served on the council of the American Academy of Ophthalmology and Oto-Laryngology and of the Association for Research in Ophthalmology. With the late Dr. Walter B. Lancaster and Theodore L. Terry, he was a co-founder of the Ophthalmological Study Council. In his native New England, he served as president of the New England Ophthalmological Society and in many important positions in the state of Maine. In his native city he founded the first sight-saving class and always took an active interest in local civic and religious affairs. This brief list of the principal offices he held attests an unselfish devotion to ophthalmology.

In spite of the demands of a busy practice and his many official duties, Dr. Beach found time to contribute many articles to ophthalmological literature. His many papers on refraction reflected his continued interest in this subject, and his book "Principles of Refraction" sums up a long experience.

A clear and forceful speaker, his papers at ophthalmological meetings were always a pleasure to listen to, not only for their content but for his lucid manner of presentation. He was a frequent discusser of other papers at ophthalmological

meetings, and his discussions were always brief and to the point. He also did his share as guest speaker at various local ophthalmological meetings over the country.

Few American ophthalmologists enjoyed a wider circle of friends, local and national. When during his last illness he made a special effort to attend a meeting of the New England Ophthalmological Society, all members spontaneously rose to their feet when he entered the room.

SYLVESTER JUDD BEACH, M.D.
1879-1953

Though Dr. Beach did not have access to a university teaching center, nevertheless he left his mark on American ophthalmology, a mark not often equaled. In his death American ophthalmology has lost an important figure.

PAUL A. CHANDLER, M.D.

News and Comment

GENERAL NEWS

American Academy of Ophthalmology and Otolaryngology.—The Home Study Courses in the basic sciences related to ophthalmology and otolaryngology, offered as a part of the educational program of the American Academy of Ophthalmology and Otolaryngology, will begin on Sept. 1 and continue for a period of 10 months. Registrations must be completed before Aug. 15. Detailed information and application forms may be secured from Dr. William L. Benedict, executive secretary-treasurer of the Academy, 100 First Ave., Bldg., Rochester, Minn.

PERSONAL NEWS

Appointment of Dr. Harold G. Scheie.—Dr. Scheie has been appointed Professor of Ophthalmology at the University of Pennsylvania School of Medicine, effective March 1, 1953.

Books

Current Therapy—1953. Edited by Howard F. Conn, M.D. Price, $11. Pp. 835. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1953.

As in the other volumes of this useful book, an attempt has been made to bring information needed by the practicing physician from all authoritative sources in a form practicable for his use. Occasionally several methods are presented for the treatment of a specific disease, and, while these methods may represent different views of therapy or different conceptions of the disease, each is the opinion of a recognized authority.

The list of contributors is a notable one, ophthalmology being represented by P. J. Leinfelder, professor of ophthalmology at the University of Iowa. There is no single chapter on the treatment of diseases of the eyes, with the exception of a small section on the treatment of retrobulbar and optic neuritis, written by Dr. Leinfelder and Dr. Bernard Alpers, professor of neurology at the Jefferson Medical College, Philadelphia. However, throughout the book there is much valuable information for ophthalmologists in the treatment of many ocular conditions.

The present volume conforms to the same high standards as the previous ones, and is recommended as a handbook of therapy.

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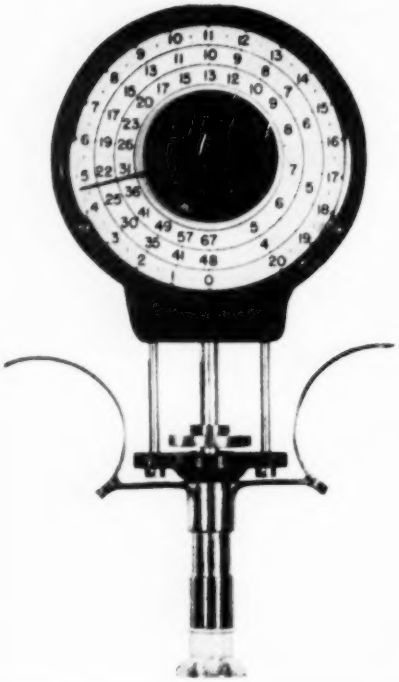

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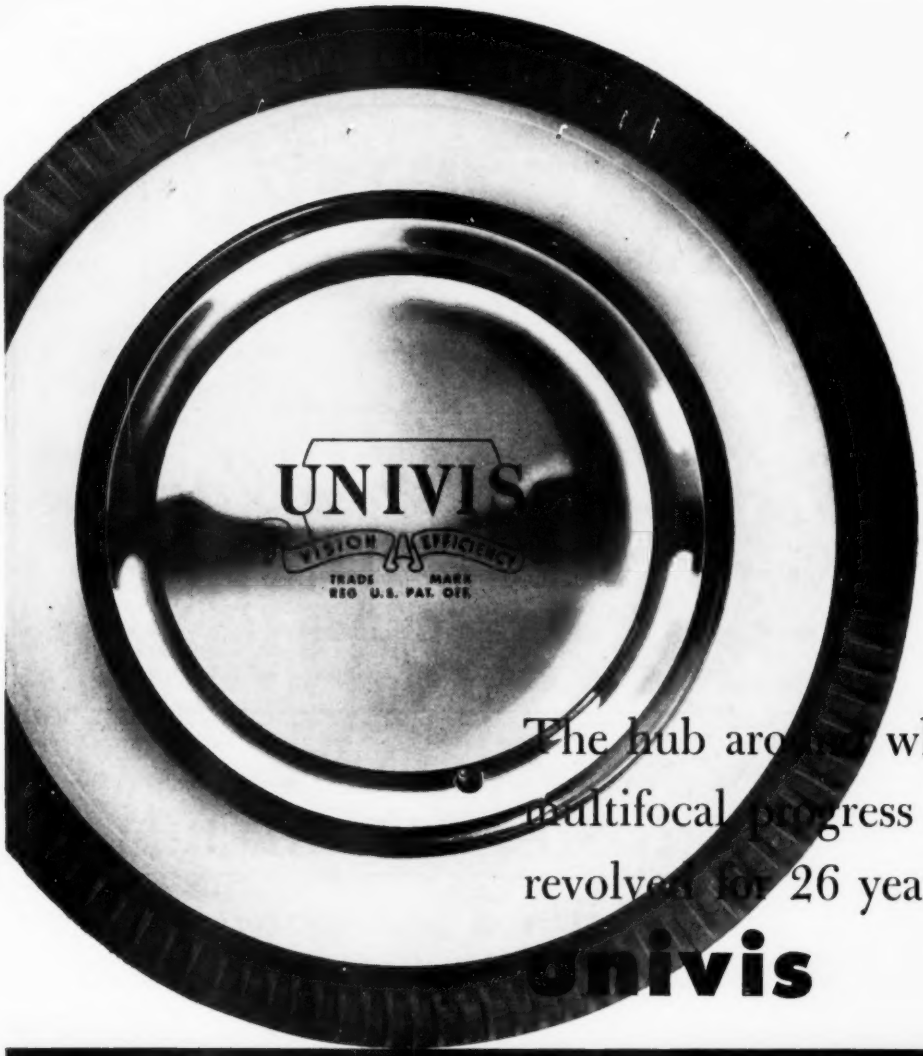

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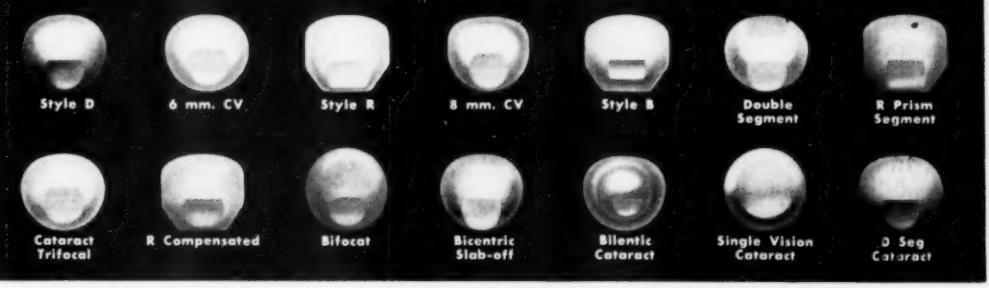

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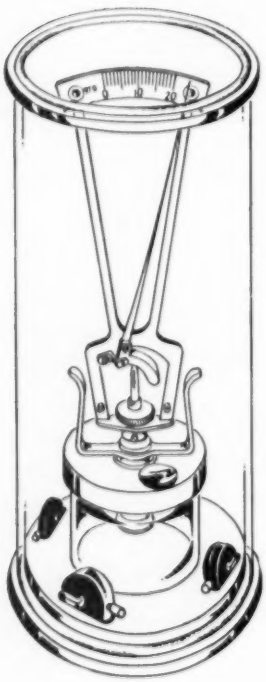

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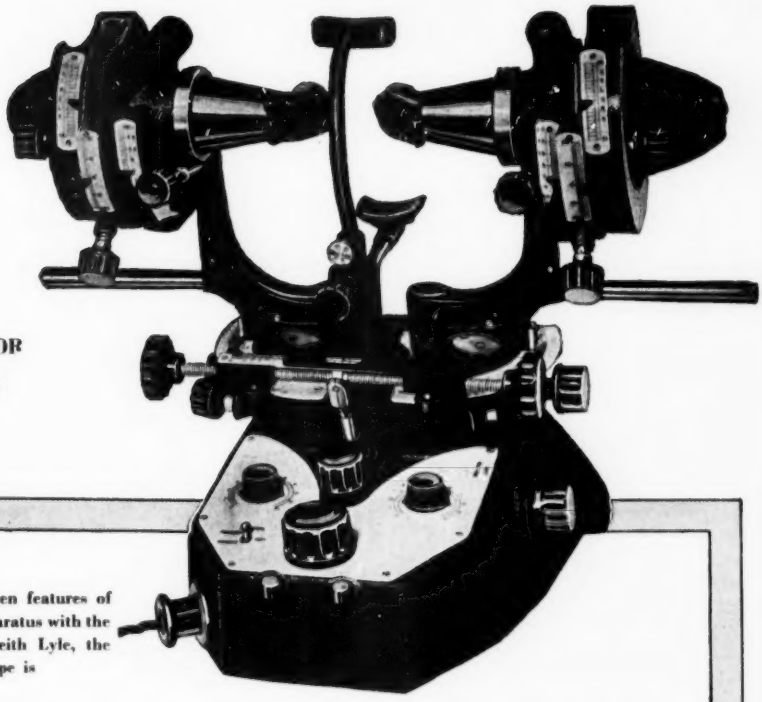

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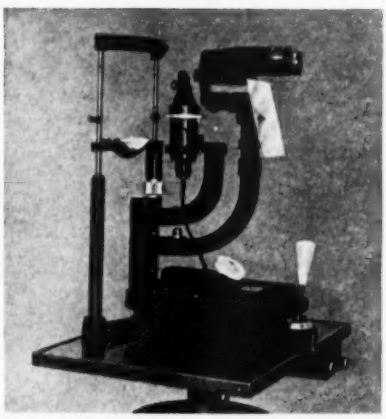

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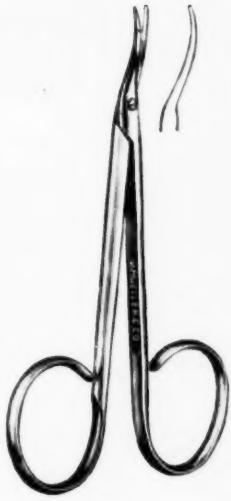

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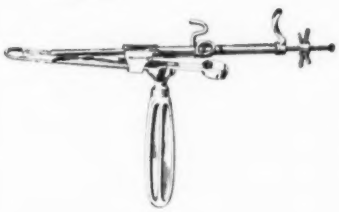

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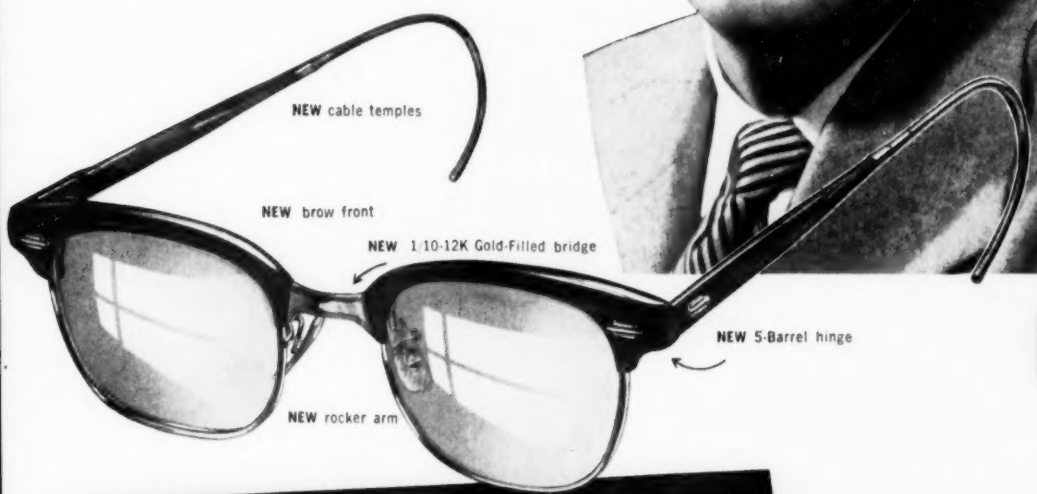

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